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THE RESPIRATORY DEAD SPACE

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A correct estimation of the volume of the respiratory dead space is of fundamental importance in connection with many of the problems of the regulation of breathing and related topics. The interpretation of the data accumulated by many investigators depends upon the decision of the question whether the dead space is a fixed or a variable quantity. If the latter is the case, what are the nature, cause, and mode of control of such variations?

Although earlier investigators recognized the dead space as a factor in breathing,[1] Loewy,[2] seems to have been the first to report a measurement of it. By means of a plaster cast of the cavity of the mouth, pharynx, trachea, bronchi and bronchioles of a cadaver he found a volume of 144 cc. He noted, however, that in the living subject even in an expiration much smaller than the volume of the dead space there are always to be found considerable amounts of CO_2, and that as expiration progresses the percentage of CO_2 in successive portions increases gradually, not abruptly: facts which later investigators have not always kept in mind.

Basing their opinion upon these observations, Zuntz and his collaborators in their extensive investigations have assumed the dead space to be an unvarying volume—the same no matter whether the subject were at rest, or breathing deeply from physical exertion, or on a mountain. All of their calculations of the alveolar ventilation and of the composition of the alveolar air involve this assumption. The method employed by them was based on the proportion: the composi-

tion of the alveolar gases (i.e., the excess of CO_2 over, or the deficiency of oxygen under, the inspired air) is to the composition of the (total, mixed) expired air as the tidal volume is to the tidal volume minus the dead space. It is noteworthy that by this method the constancy of composition of the alveolar air was not discovered. As Haldane and his co-workers have demonstrated that such a constancy normally exists, the natural inference is that the dead space is of widely varying volume.

This inference was followed up by Douglas and Haldane[3] who found when the subject was at rest a volume of 160 cc., and a progressive increase with physical exertion up to more than 600 cc. Their method was based (as all indirect determinations must be) upon the same proportion as that used by Zuntz, Loewy and others, but with this difference that Douglas and Haldane, instead of assuming the dead space and calculating the alveolar gases, have determined the composition of the alveolar air by direct analysis, and calculated the dead space. The other terms in the proportion are the (mean) tidal volume as determined from the total volume of air expired into a Douglas bag in a certain number of breaths, and the composition of this expired air.

Even before this work of Douglas and Haldane, Siebeck,[4] had found that during the hyperpnoea of physical exercise the dead space is increased. He used a method involving only a single breath—instead of the average volume of a series of expirations—in which 500 cc. or 1000 cc. of hydrogen were inspired, and then expired into a gasometer. The percentage of hydrogen in the alveolar air (from a sample at the end of expiration), the percentage in the mixed expired air, and the volume of the expiration afforded three terms in the proportion from which the fourth, the dead space, was calculated. He concluded that the dead space is larger with the lungs inflated, and suggested that this might be due to participation of the bronchi in the respiratory movements. Thus far, as we believe, Siebeck was correct. He concluded also, however, that the depth of breathing does not influence the dead space, and that it is even decreased during the deep breathing caused by inhaling CO_2. On these points we think that Siebeck was misled by not using sufficiently deep inspirations.

The latest considerable contribution to the problem of the dead space has been made by Krogh and Lindhard.[5] They have returned emphatically to the doctrine of a dead space of unvarying volume. They first subjected the method of Siebeck to a decidedly damaging criticism, and then adopted it themselves and founded quite precise conclusions

upon it. They have recently published a number of papers containing a large amount of data on various respiratory problems. In the interpretation of their data they have used a fixed dead space, and, as they themselves have remarked, if the dead space is a variable they will have to recalculate all of these experiments, and reconsider their arguments.

As we shall show that the dead space is a variable, it is of interest to note how Krogh and Lindhard were caught in a trap set (quite unintentionally) by Douglas and Haldane. The latter suggested that the enlarged dead space, which they found during hyperpnoea, serves to facilitate the flow of air, and is due to an active broncho-dilatation under the influence of nervous or chemical stimuli.[6] This highly teleological suggestion has not, so far as we can discover, led Douglas and Haldane into any error of fact, but it has led Krogh and Lindhard to confuse the question of an augmented dead space with the quite distinct problem of an active broncho-dilatation.

Accordingly, Krogh and Lindhard, in testing the volume of the dead space at rest and after exercise, seem to have arranged intentionally that the subject should take no deeper inspiration under one condition than under the other. The two measurements were equal; and they concluded therefore (correctly) that there is no evidence of active, teleological, broncho-dilatation during exercise. They did not, however, make adequate tests of the volume of the dead space in breaths as deep as occur during hyperpnoea. If they had, they would doubtless have found, as we do, a dead space varying up to as great a maximum as Douglas and Haldane claim.[7]

The true explanation of these variations is in the main, we believe, that during extra deep breathing the bronchi and bronchioles are dilated passively with the rest of the lungs. Thus a deep inspiration involves an increased dead space no matter whether the subject is at rest or exercising. We recognize, of course, that broncho-dilatation and constriction are functions under sympathetic or autonomic control, that they are influenced by drugs, and are subject to pathological disturbances.[8] Our results demonstrate merely that the ordinary variations of the dead space as between quiet and deep breathing are not for the most part of this active character.

Axial flow of gases through the tubes. As several of the recent investigators in this field have evidently left out of account the peculiarities of the movements of liquids and gases in tubes, we may begin the report of our data with a few simple experiments on this topic. They illus-

trate why it is that with a dead space of 150 cc. the first 150 cc. expired (or even the first 50 cc.) are not free from a considerable admixture of pulmonary air. They afford the reason why a dog during heat polypnoea may have a tidal volume considerably less than the volume of the dead space. They suggest that, during rapid shallow breathing in man, what we may call the physiological dead space is a much smaller volume than the anatomical dead space of Loewy's plaster cast. There may easily be a gaseous exchange sufficient to support life even when the tidal volume is considerably less than the dead space.

If one takes a glass tube of, say, a meter length and one or two centimeters bore, and blows tobacco smoke into one end, he sees that the smoke does not move along the tube in a cylindrical column, filling the tube from side to side, but in the form of a very thin spike. If the tube is held vertically, so that gravitational effects are avoided, the spike follows the axis of the tube, and the tip of the spike begins to issue from the upper end before the tube as a whole is more than a quarter or a third filled with smoke. The quicker the puff, the thinner and sharper the spike, and the more smoke must be blown through before all the clear air is washed out.

If, at the moment that the tip of the spike reaches the upper end of the tube, the puff is stopped by applying the tongue to the lower end, the spike breaks instantly everywhere; and the tube is seen to be filled from side to side with a mixture of smoke and air, thin at the upper end, a thicker mixture at the lower, and all gradations between.

If now an inspiration is made, a thin spike of clear air projects itself down along the axis and into the mouth of the operator along with some of the thicker mixture in the lower end of the tube.

An even more striking demonstration is obtained with a glass bulb having inlet and outlet tubes on opposite sides. When smoke is blown in through one of these tubes, the column at first shoots across the centre of the bulb and out through the other tube with little contamination of the clear air surrounding the stream. If it is stopped suddenly, a complete mixing of smoke and clear air occurs almost instantaneously, and thereafter a very large volume of air must be drawn through the bulb before the last trace of smoke is washed out.

For instrumental purposes these frictional effects are easily neutralized by filling the large glass tube with some loose fibrous material such as glass wool, jute, disks of wire gauze, etc. The friction being then the same at every point in the cross section, the column of smoke pushes the air ahead of it like the plunger of a pump. This holds true even

when the fibrous material is so loosely packed as to afford no noticeable resistance to an expiration.

We have employed a tube of this sort to determine the composition of successive fractions of an expiration. At intervals along the tube were inserted side tubes to which were connected small pipettes of a type described in a previous paper from this laboratory.[9] The apparatus is shown in figure 3, and examples of the results obtained in figure 4. From them it is clear that in a quick expiration through the mouth the "spike" of alveolar air begins to issue between the lips with the first 25 to 50 cc. of air expelled. They show also that for an approximately complete washing out of the dead space, so that the last portion shall consist of practically undiluted alveolar air, an expiration (especially

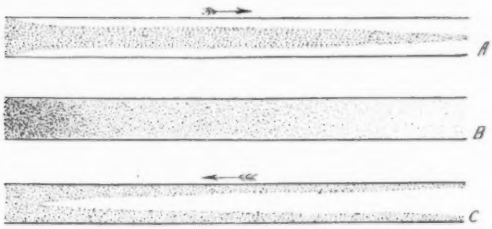

Fig. 1

Fig. 2

Fig. 1. (*a*) Shows a "spike" of smoke moving through a glass tube. (*b*) Shows the condition when the current is suddenly stopped and mixing instantaneously occurs. (*c*) Shows clear air drawn in.

Fig. 2. Shows how a column of smoke crosses a bulb with little mixing or sweeping out of the air within it.

if rapid) of at least 400 cc. or three times the volume of the dead space is required. This applies to ordinary quiet breathing. During hyperpnoea the larger dead space necessitates a much greater expiration before an undiluted sample of alveolar air can be obtained.

We have used and compared five methods with minor variations for determining the dead space:

First, or CO_2 *method.* The subject began with the deepest possible expiration with the mouth open, and followed this with an inspiration sufficient in volume to fill the dead space with entirely fresh air. In some cases this breath was held for seven to ten seconds; in others the next act followed immediately. This consisted in the subject making the deepest possible expiration through a rubber tube into a gasometer

or rubber bag. The subject then kept his tongue against the end of the tube until it was closed with a spring clip. A sample of alveolar air was drawn from the tube as in the method of Haldane and Priestley, and its CO_2 percentage (a_1) was determined with a Haldane apparatus. (The little apparatus graduated up to 10 per cent for CO_2 only is most convenient for this purpose.) A sample of the mixed air (m_1) in the gasometer was also analyzed. The volume of the (second) expiration

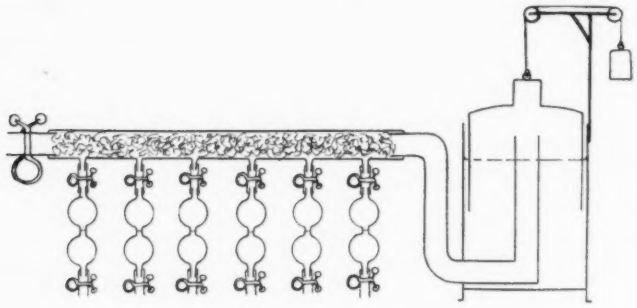

Fig. 3

Fig. 3. Apparatus for analyzing successive portions of an expiration. The volume expired is measured by means of the gasometer. The tube (volume 400 cc. and length 100 cm.) is filled with loosely shredded glass wool or jute. The pipettes hanging from it are filled with $\frac{1}{10}$ normal baryta. Immediately after an expiration the clip at the end of the tube is closed. By opening the clips on the pipettes, exactly one-half (15 cc.) of the baryta is then allowed to run out of each, thus drawing in a sample of air from the tube. The clips are reclosed, and the remaining half of the baryta is thoroughly shaken with this air, and is then drained into a small flask, and tightly stoppered. After complete sedimentation of the $BaCO_3$, a sample (5 cc.) of the supernatant baryta is titrated with $\frac{1}{10}$ normal acid; and, with corrections for the barometric pressure and temperature when the air sample was taken, its CO_2 percentage is calculated.

(E) was read from the gasometer, or by means of a gas meter connected with the rubber bag. The dead space (d) of the apparatus, i.e., the volume of the tube, was determined once for all. It should be as small as convenient. By using a readily collapsible tube, or by filling the tube with water before each experiment, it can be eliminated entirely. Although more exact these arrangements are also more trouble and not necessary.

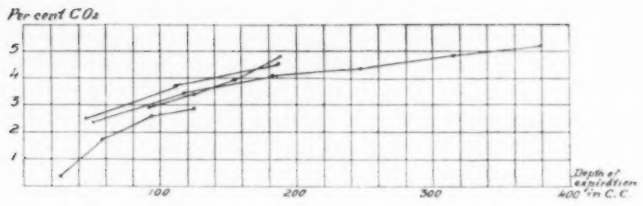

Fig. 4

Fig. 4. Showing the percentages of CO_2 in successive portions of quick expirations in four experiments with the apparatus of figure 3.

The (virtual) dead space (D_1) for CO_2 was calculated from these data by the formula:

$$D_1 = E - E\frac{m_1}{a_1} - d$$

It is not necessary that the alveolar samples should have a normal CO_2 content, as it is not the absolute amount but the relation of this factor to the CO_2 in the mixed air which counts. For instance, in two experiments (on Y. H.) the data and results were:

E	A_1	M_1	d	D_1
3810	3.75	2.90	195	670
3850	6.20	4.70	195	665

The characteristics of the results obtainable with this method are shown by figure 5.

These data and their significance may be summarized as follows: (1) The dead space as determined by this method (without a pause) varies with the extent to which the lungs are inflated. Below the inflation of quiet breathing it may be as small as 60 cc. or less. At the normal level volumes of 150 or 160 cc. are obtained in close agreement with other observers. When the lungs are inflated to an extent corresponding to that of hyperpnoea, the volumes are much larger (up to 600 or 700 cc. or more). But they are the same no matter whether the subject is at rest or exercising. This indicates that the increased dead space observed by Douglas and Haldane under the latter condition is chiefly a mere mechanical stretching, not an active broncho-dilatation.

(2) When inspiration is as far as possible of a costal character, the

values obtained even by fairly great inflation (3100 to 3800 cc.) are only about half as large as when it is of the ordinary diaphragmatic character. This indicates that the expansion of the dead space between ordinary and deep breathing depends to a great extent upon the lengthening of the bronchi and bronchioles with the downward movement of the diaphragm.

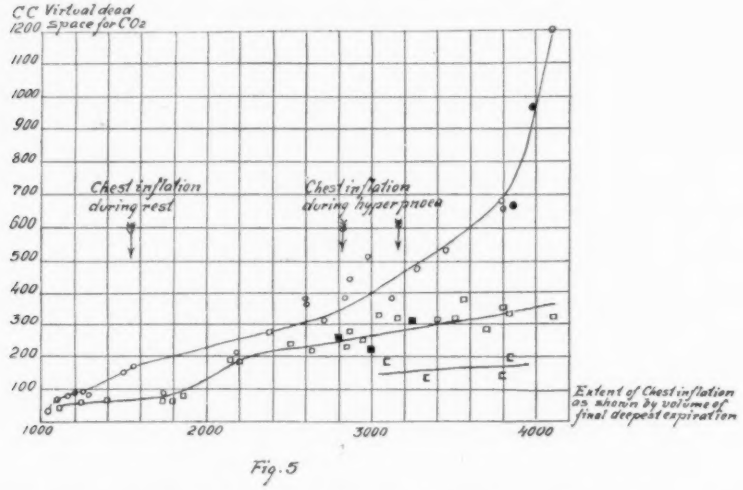

Fig. 5

Fig. 5. A diagram of results obtained by our first method. Ordinates express the (virtual) dead space, and abscissae the extent to which the lungs were expanded above the residuum at deepest expiration. In the subject (Y. H.) during quiet breathing with a tidal volume of 500 cc. inspiration reaches a level of about 1600 cc. as indicated by the arrow at the left, and an active hyperpnoea raises the level to between 2900 and 3600 as indicated by the arrows at the right.

The values for the dead space when the final expiration was made immediately after the inspiration are indicated by the little circles (o)., and upper line.

The values obtained when the inspiration was held for seven to ten seconds are expressed by the little squares (□) and the middle line.

The influence of making the inspiration and pause so far as possible with the costal mechanism without contraction of the diaphragm is shown by the incomplete squares (⊏) and the lower line.

All of the foregoing observations were made while the subject was at rest, sitting on a stool in a room of comfortable temperature. The solid circles and squares (● ■) on the contrary express observations by identical procedures, but taken while the subject was hyperpnoeic from vigorous exercise on a stationary bicycle. As they correspond closely with the observations during rest, they show that the increased dead space during exercise is not due to active bronchodilatation, but to passive distension incident to deep inspirations.

(3) When the inspired air is held for seven to ten seconds before the final expiration is made, the values obtained for the virtual dead space are at all levels of chest inflation considerably smaller (less by a third to one-half) than when no pause is made. This is probably due to diffusion of CO_2 in appreciable amounts through the mucosa of the mouth, trachea, bronchi, etc. (A study of the diffusion of CO_2 and oxygen in the mouth is now under way in this laboratory, has afforded confirmation of this view, and will be reported in a later paper.)

Second, or oxygen method. The procedures were the same as in our first method except that the gas samples were analyzed for oxygen and the percentages found (m_2 and a_2) were subtracted from the oxygen percentage of the inspired air. Thus the dead space for oxygen (D_2) was found by the formula

$$D_2 = E - E\frac{20.93 - m_2}{20.93 - a_2} - d$$

It is noteworthy that when both this and the CO_2 method were carried through on the same breath *the (virtual) dead space for CO_2 was always smaller than that for oxygen.* The difference between them was greater (owing to the fact that D_1 was reduced much more than D_2) when the breath was held for several seconds than was the case when no pause was made. For example we found (on J. L. W.):

	E	D_1	D_2	$D_1 : D_2$
With pause.....	720	33	78	42:100
With pause.....	1450	66	192	34:100
With pause.....	3430	569	1020	55:100
Without pause.....	(800)	130	154	84:100
Without pause.....	(1450)	156	164	95:100
Without pause.....	(3000)	563	809	69:100

The last three experiments here instanced were really made with our fourth and fifth methods which give the average dead space for a series of breaths. But they suffice to show that the difference between D_1 and D_2 is much less without, than it is with, a pause. From this fact as from the evidence of the first method above discussed, it is clear that *there is a very considerable diffusion of CO_2 from the walls of the respiratory passages.* The oxygen exchange on the other hand between the air in these tubes and the blood in their walls is comparatively small. It is probable that the great part of the blood affected by this

diffusion is not in the pulmonary, but in the systemic circulation and flows from the bronchial veins to the right heart.*

This bronchial CO_2 diffusion affords an explanation of the fact that the respiratory quotient calculated from alveolar analyses is always lower than that found from the total expired air. Indeed this explanation was pointed out to one of us some years ago by Dr. J. S. Haldane,[10] and it was his forecast which led us to look for a smaller (virtual) dead space for CO_2 than for oxygen.

Third, or hydrogen method. This is the method of Siebeck as employed by Krogh and Lindhard. In our use of it we made a pause of some six to eight seconds before the final expiration. We also varied the depth of the inspiration, the point which, as already explained, Krogh and Lindhard overlooked. In several experiments we determined on a single breath the dead space, both for oxygen and for hydrogen. The formula for the method, in which H is the percentage of hydrogen in the gas inspired, m_3 and a_3 are the percentages of hydrogen in the mixed and alveolar samples, and the other terms, as in previous formulae, is

$$D_3 = E - E\frac{H - m_3}{H - a_3} - d$$

Our results with this method are given in the fourth column of the table of comparative results.

The dead space for hydrogen is, in general, of approximately the same size as that for oxygen. Like that both for oxygen and for CO_2, it varies with the extent to which the lungs are inflated. These observations do not, however, invalidate the demonstration of Krogh and Lindhard that with breaths of the same size the dead space is the same during exercise as during rest.

Fourth and fifth, or Douglas bag methods. The fourth method which we used was identical with that of Douglas and Haldane. The total expired air for a certain length of time was caught in a Douglas bag and measured. This volume was divided by the number of breaths made in the period to find the mean volume of expiration (e). A sample was analyzed for CO_2, and a separate determination of the subject's alveolar air was made. The formula was the same as that for our first method, except that the mean tidal air (e) replaces (E)

*Since this paper was written, correspondence with Dr. Haldane has changed our opinion on this point. The greater part of this blood must go into the pulmonary veins and to the left heart. See note at the end of this paper.

the deepest possible expiration. The extent of the lung dilatation (E) when needed, was determined separately with a small graduated spirometer.

The fifth method was the same as the fourth except that oxygen analyses also were made on the expired and alveolar air. The formula was the same as for our second method with (e) substituted for (E).

With these methods the dead space for oxygen was always larger than that for CO_2. But as there was no pause between inspiration and expiration the differences were not nearly so great as between the results of the first and second methods with a pause.

The effects of exercise (fast walking) were found, in agreement with the observations of Douglas and Haldane, to include a considerable increase in the dead space. But this was not to any considerable extent assignable to active broncho-dilatation, for it was of practically the same amount as that obtained by the other methods with equal chest inflation while the subjects were at rest. Furthermore, with the bag methods when the subject sat perfectly still and voluntarily made deep, but slow breaths, the dead space worked out to a volume as great as, or greater than, that during the hyperpnoea of exercise. For example, the dead space for CO_2 and for oxygen (D_4 and D_5) were found (on J. L. W.) to be:

	TIDAL AIR	D_4	D_5
At rest, shallow breathing with constricted chest	180	130	154
At rest, natural breathing	403	189	198
Fast walking and natural hyperpnoea	1373	407	650
At rest, deep slow breathing	1384	563	809
At rest, deep slow breathing	2116	917	1237

Comparative results. In the table of comparative results are shown data for a single subject by all five methods. The first column indicates the extent to which the lungs were dilated above deepest expiration. In this subject when seated and breathing quietly the tidal air amounted to 400 or 450 cc. In ordinary inspiration his lungs were dilated to 1400 or 1500 cc. above deepest expiration. The "vital capacity" was 3800 or 3900 cc. The data of the fourth and fifth methods are inserted at places in the table corresponding to the extent to which the lungs were expanded at inspiration.

Table of comparative results of determinations of the volume of the dead space of a single subject (J. L. W.) by five methods (D_1 to D_5) arranged according to the extent to which the lungs were dilated (E)

E	D_1	D_2	D_3	D_4	D_5	
			cc.			
720	33	78				
725			138			Below level of normal breathing, i.e., with contracted chest.
860	58					
				130	154	
				154	163	
				132	154	
1450	66	192				
				189	198	At level of normal breathing.
1480			102			
1500	191	296				
1650	82	245				
1710	86	186				
1860		370	267			
2430			139			
2540	156					
2710			234			
2770	290					
				407	650	At level of hyperpnoea of vigorous exercise.
				563	809	
3220		1116	1105			
3400			653			
3430	569	1020				
3450		847	725			
3460	289	620				
3550	406					
3580			928			
3620	796	1212				
				917	1237	

The table clearly demonstrates by all methods the passive dilatation of the dead space with chest expansion. It shows the diffusion of CO_2 from the walls of the dead space by the facts that the figures for D_4 are somewhat smaller, and those for D_1 (with a pause) are very much smaller, than those obtained by the hydrogen (D_3) and the two oxygen methods (D_2 and D_5).

There is also to be noted a contrast between the first three methods (on single breaths) and the fourth and fifth (with the Douglas bag) in that, while the latter increase fairly uniformly, the former are quite

irregular. These discrepancies are not due to analytical errors which can scarcely exceed 10 per cent (except possibly in the third, or hydrogen method, where they may reach 20 per cent), nor to variations in the final measured expiration which should not err more than 100 or 200 cc. in totals of from 1000 to 4000 cc. They are due to the fact that, while the fourth and fifth methods give the mean dead space for several minutes, the first three methods determine it at a single instant. This suggests that the dead space is continually undergoing active variations which are recorded by our first three methods and averaged by the last two.

Rhythmic variations in the dead space. When one makes a series of determinations at regular intervals by any one of our first three methods on a single subject under conditions and at a chest expansion as nearly uniform as possible, it seldom happens that any two successive results agree to within even the extreme errors of the method. This fact which we have verified repeatedly puzzled us even after many months had been spent in unravelling the influence of chest expansion on the dead space. The suggestion was made to us by Dr. A. L. Prince of this laboratory that there might be variations of tonus in the non-striated muscle fibers of the bronchi similar to those in other organs containing such tissue. A survey of the literature shows that Einthoven[11] many years ago observed slight rhythmic variations of bronchial tonus in dogs, although more recent investigators seem not to have noticed them.

Accordingly we carried through by our first method two series of observations (on J. L. W.) in which the dead space was determined every three minutes for more than an hour.* The results are shown in figures 6 and 7. In figure 6 are to be seen rhythmic variations of a periodicity of about 7.5 minutes, large waves amounting to thirty or forty per cent of the whole volume of the dead space alternating with waves only half as large. In figure 7 the results obtained on the same subject the next day exhibit equally marked variations, but of slower and less clearly marked periodicity.

We may fairly conclude from these experiments, supported by a mass of observations too voluminous for detailed publication, that *the respiratory dead space, like other cavities having non-striated muscle fibers in their walls, is subject to considerable active variations of a more or less rhythmic character.*

*We are indebted to Dr. Prince for assistance in carrying out the necessary rapid succession of analyses.

Reflex influences of close and fresh air on bronchial tonus. One of us (Y. H.) is very susceptible to the ill effects of a close and crowded room. The nasal mucosa becomes congested almost to the occlusion of the nostrils, and asthmatic sensations also develop. On going out of doors, or feeling a cool breeze on the face, there occur a reflex constriction of the nasal blood vessels, and an ease of breathing, after a few deep breaths, suggestive of an active reflex change from constriction to dilatation of the bronchi. The stimulus seems to be the cool sensation from the face. The effect is too rapid to depend on body temperature. Sensations of "stuffiness" and obstructed breathing have been noticed also in a crowded railroad car when there was no perceptible perspira-

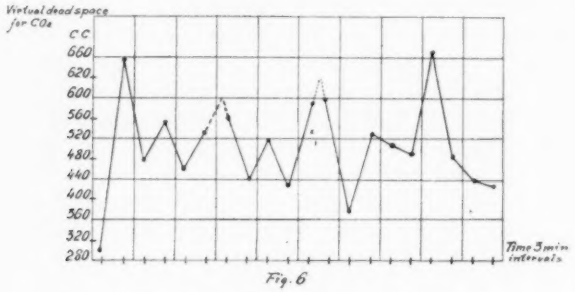

Fig. 6

Fig. 6. A series of dead space determinations (averaging 500 cc.) at intervals of three minutes for over an hour made by our first method on J. L. W. The chest expansion was as nearly uniform as possible: averaging 3300 cc. for E. Active variations in the volume of the dead space are here seen to occur rhythmically, large waves alternating with small at intervals of about seven and one-half minutes.

tion, no impression of being too warm, and occasionally even when it was rather too cold for comfort. We have noticed also that in a Turkish bath, persons who are unaccustomed to it, or who do not perspire readily, may experience obstructed breathing, nausea and faintness, while the practiced bather breathes quite easily and feels exhilarated. The same holds true, however, in a steam room (Russian bath) with an atmosphere at 45° C., and saturated with moisture. Under the latter conditions body temperature must rise practically equally whether one perspires or not. The obstructed breathing, if it is a broncho-constriction, together with the nausea and faintness, appear to us, there-

fore, to be rather due to reflexes from the skin than to the central effects of hyperthermia.[12]

Early in these investigations there were carried out on Mr. Edmund Andrews, then a student in this laboratory, a series of observations which indicated *that in a "close" room with a distinct feeling of stuffiness the dead space is abnormally small; that standing in an agreeably cool breeze from an open window for even a few seconds induces an enlargement; that a distinct chill on the contrary induces in one coming from a close room, not an increase, but on the contrary a further decrease in the volume of the dead space—in one case the subject "caught cold;" and that a warm room with no sensation of stuffiness but free perspiration tends to cause enlargement of the dead space.* The methods employed for these observations were crude (the apparatus shown in figure 3 was used) and

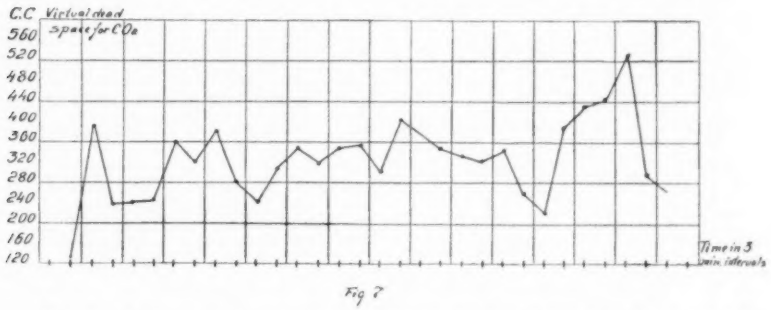

Fig 7

Fig. 7. A series of observations similar to those in figure 6 on the same subject the next day. The rhythm is much less regular. The mean (330 cc.) of these determinations is less than before because E was smaller, averaging 2650 cc.

we had not then puzzled out the relation of the volume of the dead space to chest inflation. The observations are, however, worthy of record as a starting point for future investigations.

Using our second method and expirations as nearly equal as possible (3260 and 3140 cc.) we found the dead space (in J. L. W.) in a close room to be 645 cc. and a few minutes later out of doors—air cool and dry, and sky clear—a volume of 816. Owing, however, to our demonstration of the type of variations discussed in the preceding section, it will require many additional observations to settle the point as to whether this really indicates broncho-dilatation.

We have, however, carried out several experiments on the influence upon the dead space of steam, hot air, and cold shower baths. The

results are rather discordant, although they suggest that when one begins taking such baths the hot rooms cause broncho-constriction, and the cold shower a dilatation, but that after a little practice reactions of the opposite type occur. Our initial experiments on the effects of the hot room (65° C. with dry bulb thermometer and 37° with wet bulb), steam room (44° C. with both wet and dry bulb thermometers), and cold shower (16°) of a Turkish bath gave the following results for the oxygen dead space (D_2) at nearly uniform chest inflation (E):

SUBJECT	Y. H.	J. L. W.
E_1 or amount of lung inflation	3150–3320 cc.	3340–3650 cc.
D_2 in cool well ventilated room	230	1346
D_2 after fifteen minutes in steam room	104	218
D_2 after fifteen minutes more in hot room		
D_2 after cold shower		634
D_2 after dressing cool room	338	1124

A few days later, the following results were obtained.

SUBJECT	Y. H.	J. L. W.
E_1 or amount of lung inflation	3650–4100 cc.	3550–3800 cc.
D_2 in cool dressing room	300	505
D_2 after ten minutes in steam room	385	777
D_2 after ten minutes more in hot room	752	1288
D_2 after cold shower	234	557
D_2 after dressing in cool room	360	1270

One experiment on this topic was made also with the Douglas bag methods. It showed that (in J. L. W.) after ten minutes in the steam room and similarly in dry heat the (virtual) dead spaces for CO_2 and for oxygen were 200 cc. and 396 cc. respectively, as compared with 189 cc. and 198 cc. when the subject was sitting in a room of ordinary temperature. But the volume of air breathed per minute, and the tidal volume were about twice as great in the hot rooms as in the cool, so that the chest inflation (which we failed to measure) was probably enough to balance to an unknown extent the apparent broncho-dilatation. This incomplete experiment, however, yielded one new observation: it indicated that *in great heat the exhalation of CO_2 from the walls of the dead space is enormously increased. This may well be due to an active hyperaemia.* This exhalation is shown in the fact that although

the subject was breathing twenty times a minute the virtual dead space for CO_2 (D_4) was only half of that for oxygen (D_5). In agreement with the observations of Haldane,[13] the alveolar CO_2 was considerably lowered. The respiratory quotient for the mixed expired air was 0.928, while the quotient calculated from the alveolar air was only 0.717: an extraordinary difference.

The dead space in asthma. Some observations on asthmatic subjects (by F. P. C. at the Tulane Medical School in New Orleans) show dead spaces (D_1) smaller than in normal subjects although not to the extent expected.[14] It is very probable, however, that their chests were dilated much above the normal level and that they failed to make expirations of normal depth in the tests. When these measurements were made, we were still unaware of the influence of chest expansion on the dead space. Assuming their chests to have been expanded to the extent of 1000 or 1500 cc. above the normal their dead spaces were only about one-third of that of normal subjects at such chest expansions. *It appears probable that in asthmatics the abnormally expanded condition in which the chest is held affords a passive stretching of the bronchi and bronchioles which partially compensates for the active bronchoconstriction.*

CONCLUSIONS

From a consideration of the axial flow of gases through tubes, and from determinations of the CO_2 content of successive fractions of the expired air it is found that in man some alveolar air (i.e., CO_2 in increasing amounts), begins to issue from the nose and mouth even in the first 50 cc. of an ordinary expiration. A tidal volume even much smaller than the volume of the dead space may thus afford a very considerable gaseous exchange, as in animals during heat polypnoea. With the ordinary expansion of the chest during quiet breathing an expiration of at least 400 cc. is necessary to effect an even approximately complete washing out of a dead space of 150 cc. During hyperpnoea a much larger expiration is necessary before a sample of pure alveolar air is obtainable.

Five methods of determining the dead space on man have been employed with generally concordant results and some significant differences. The results show that the dead space expands and contracts passively with the movements of the thoracic walls and lungs. At the level of ordinary breathing the dead space is about 150 cc. (as practically all previous observers have found). At shallower levels, it is, however, considerably less; with deeper breathing it is much

more (400 to 600 cc.); and with the deepest breaths the (virtual) dead space may exceed a liter in volume. It is much more affected by diaphragmatic than by costal movements.

The dead space is found to be of practically the same volume during rest and exercise, providing that the determinations are made at equal extents of chest inflation. This fact indicates that the enlargement of the dead space during hyperpnoea is essentially a passive stretching and not an active broncho-dilatation.

The dead space for oxygen is always larger than that for CO_2. This is shown to be due to the diffusion of CO_2 in considerable amounts from the walls of the mouth, trachea, bronchi, etc.

The dead space, even at a uniform extent of chest inflation, is continually undergoing active variations in volume. At times these variations exhibit a distinct rhythm of a period of several minutes. They may amount to as much as 30 per cent of the mean volume of the dead space in quiet breathing.

Some facts are reported which suggest that in a "close and stuffy" room the bronchi, etc., are constricted, and that a distinct chill constricts them further, while pleasantly fresh cool air, on the contrary, induces broncho-dilatation. Experiments in a Turkish bath have not, however, afforded concordant results, except that they have shown that during profuse perspiration and cutaneous hyperaemia there is a greatly augmented diffusion of CO_2 from the walls of the dead space. This doubtless indicates a hyperaemia of the respiratory passages. As a part of the CO_2 given off in the passages is inspired into the alveoli before being expired, and as the alveolar respiratory quotient may be only a little above 0.7 when the quotient of the mixed expired air is considerably above 0.9, it appears that under such conditions as much as one-half of the total CO_2 exhaled by the subject may come from the dead space.

In asthmatics, the chronic dilatation of the chest stretches the pulmonary passages passively, and thus tends to compensate to some extent for their active contraction.

NOTE: After our investigations were completed and this paper was ready for publication, one of us (Y. H.) wrote to Dr. J. S. Haldane of the results obtained. By return mail, Dr. Haldane replied that he had been at work on the same topic and had obtained practically identical results as regards the passive expansion of the dead space.

A few days later he sent to us the manuscript of his paper with the suggestion that it should either be combined with ours or pub-

lished simultaneously. As publication of the two papers uncombined appears to us to be the most effective method of carrying conviction to the minds of others, and as each paper has some special aspects, Dr. Haldane's paper (which he has curtailed and modified after reading our paper) appears elsewhere in this number of this Journal. It is certainly a rare event that investigators, working entirely independently on opposite sides of the Atlantic, reach so nearly the same conclusions on a topic which has been in a state of confusion as long as has that of the respiratory dead space. The only important point of difference, between Dr. Haldane and ourselves was as to whether the greater part of the blood, which has lost CO_2 directly to the dead space, passes to the right heart, as we supposed, or to the left heart, as Dr. Haldane suggests. In the latter case the large amounts of CO_2 given off to the respiratory passages during hyperpnoea, and especially during heat hyperpnoea and bronchial hyperaemia (see our experiments in the Turkish bath) may prove to be of great importance. After reading the papers of Miller[15] to which Dr. Haldane refers there is no doubt in our minds that Dr. Haldane is correct in considering that the passive stretching of the dead space occurs principally in the atria, and that the greater part of the blood from the dead space flows in to the pulmonary veins and left heart.

[1] For literature cf. Siebeck: Skandinavisches Archiv für Physiologie, 1911, xxv, p. 81.

[2] Loewy: Pflüger's Archiv, 1891, lviii, p. 416.

[3] Douglas and Haldane: Journal of Physiology, 1912, xlv, p. 235.

[4] Siebeck: Loc. cit.

[5] Krogh and Lindhard: Journal of Physiology, 1913, xlviii, p. 30.

[6] Cf. Campbell, Douglas and Hobson: Journal of Physiology, 1914, xlviii, p. 303.

[7] Similar observations have been made but misinterpreted by Carter.: Journal of Experimental Medicine, 1914, xx, p. 81.

[8] For literature see Jackson, D. E.: Journal of Pharmacology and Experimental Therapeutics, 1914, v, p. 479.

[9] Henderson and Russell: American Journal of Physiology, 1911, xxix, p. 441.

[10] Pike's Peak Expedition: Phil. Trans. B. cciii, p. 231.

[11] Einthoven: W. Pflüger's Archiv. f. d. gesammte Physiologie, 1892, li, p. 415.

[12] Cf. Henderson: The unknown factors in the ill effects of bad ventilation. Transactions of Fifteenth International Congress on Hygiene and Demography, 1913, ii, p. 622.

[13] Haldane: Journal of Hygiene, 1905, v. p. 494.

[14] Hoover, C. F. and Taylor, L. have reported similar observations but have interpreted them differently: Archives of Internal Medicine, 1915, xv, p. 1.

[15] Miller, W. S.: Journal of Morphology, 1893, viii, p. 165; and Anatomomische Anzieger, 1906, xxviii, p. 433.

THE VARIATIONS IN THE EFFECTIVE DEAD SPACE IN BREATHING

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In the foregoing paper by Messrs. Yandell Henderson, Chillingworth and Whitney, clear evidence is brought forward that the increase in the respiratory dead space during hyperpnoea, as noted by Douglas and myself during muscular work, and by Campbell, Douglas and Hobson for hyperpnoea caused by CO_2,[1] is due, not to active dilatation of the bronchi, as we believed, but to mechanical stretching of the lungs. I had meanwhile reached the same general conclusions, and it is unnecessary for me to repeat what my American colleagues have so admirably expressed; but as my methods differed in certain respects from theirs, and in one or two points I have been led to a different interpretation of the data, it seems worth while to put my experiments on record along with theirs.

Douglas and I obtained our results for the dead space with the existing natural breathing, deep during hyperpnoea, and comparatively shallow during rest. I had been led to suspect that the apparent divergence between our results and those of Krogh and Lindhard depended on the depth of breathing, and in order to determine the influence of varying the depth *per se*, without any hyperpnoea, I made use of the fact, discovered by Priestley and myself, that the frequency of breathing may be varied within wide limits, without altering the alveolar CO_2 percentage, provided that the depth of breathing is allowed to regulate itself naturally, with no forcing or holding back. Thus by varying the frequency one can greatly vary the depth, without altering the mean alveolar CO_2 percentage, and without true hyperpnoea being present. I have verified this on myself within wider limits than in our original experiments, in groups of experiments, the experiments in each group succeeding one another at as short intervals as possible, but the different groups being on different days.

[1] Journal of Physiology, xlv, p. 235, 1912, and xlviii, p. 303, 1914.

It was easy enough to reduce the frequency to three breaths a minute without any discomfort, provided the inspirations and expirations were sufficiently slow and regular. The results obtained were as follows:

Alveolar CO_2 percentage

FREQUENCY OF RESPIRATIONS PER MINUTE	END OF INSPIRATION	END OF EXPIRATION	MEAN
30	5.66	5.70	5.67
4	5.24	6.09	5.66
24	5.48	5.49	5.48
6	5.40	5.73	5.56
36	5.63	5.73	5.68
4	5.11	6.34	5.72
3	5.19	6.24	5.71
60	6.17	6.16	6.16

The constancy of the alveolar CO_2 percentages with frequencies of from three to thirty-six breaths is very striking. The cause of the paradoxical rise in alveolar CO_2 percentage when the frequency was increased to sixty will be discussed later.

The effective dead space was now determined by our method with varying frequencies of breathing, and consequent variations of depth, the expired air being collected over a period of three minutes, and the rate of breathing having been accurately adjusted by a clock for at least two minutes before the collection of samples was begun. Inspiration and expiration were timed to be of about equal duration and with no pause between them. For reasons which will appear below, the results, which are given in the following table, are stated somewhat fully.

This table shows clearly that in spite of the absence of hyperpnoea the effective dead space increases enormously with increased depth of breathing, the increase in dead space bearing a rough proportion to the increase in depth. This fact explains the apparent divergence between our own results and those of Krogh and Lindhard, since the latter observers made their determinations with a constant and relatively small depth of breathing.

The data for oxygen bring out a further point. It will be noticed that the differences between the oxygen percentages at the end of inspiration and end of expiration are much greater than the differences in the CO_2 percentages: also that the respiratory quotient as calculated

FREQUENCY OF RESPIRATIONS PER MINUTE	MEAN DEPTH OF EXPIRATIONS AT 37° SATURATED IN CC.	EXPIRED AIR			ALVEOLAR CO_2 PERCENTAGE			ALVEOLAR O_2 PERCENTAGE			ALVEOLAR RESPIRATORY QUOTIENT	EFFECTIVE DEAD SPACE MINUS THAT OF MOUTHPIECE, CC.	
		CO_2%	O_2%	Respiratory quotient	End of inspiration	End of expiration	Mean	End of inspiration	End of expiration	Mean		Calculated from CO_2	Calculated from O_2
3	2984	4.29	16.07	0.848	5.41	6.04	5.72	14.56	12.84	13.70	0.745	683	920
4	2438	4.56	16.91	0.875	5.24	6.09	5.66	14.98	13.07	14.02	0.814	467	619
6	1413	4.24	16.47	0.905	5.37	5.70	5.53	14.51	14.25	14.38	0.803	272	392
18.5	683	3.31	17.27	0.871	5.53	5.75	5.64					224	
17.0	650	3.59	17.01	0.887	5.63	5.79	5.71	13.95	13.74	13.84	0.762	171	223
17.7	643	3.58	16.98	0.888	5.50	5.59	5.55	13.44	13.99	13.72	0.721	161	231
24	410	3.22	17.15	0.780	5.45	5.46	5.45	13.88	13.42	13.65	0.692	111	136
60	357	1.89	18.75	0.820	5.87	6.06	5.96	13.15	12.85	13.00	0.703	185	199

from the alveolar samples is lower than the true quotient as calculated from the composition of the expired air. To the latter point and its probable explanation attention had already been called by Douglas, Henderson, Schneider and myself in our account of the Pike's Peak Expedition.[2] It follows that, as shown in the table, the effective dead space calculated from the oxygen percentages is greater than that calculated from the CO_2 percentages, my results in this respect being entirely confirmatory of those given in the previous paper.

It will also be seen that in the three experiments with normal breathing, and a depth of breathing of about 650 cc., the dead spaces found differed considerably, thus also confirming the conclusions of the previous paper.

It seemed probable to Douglas and myself that the increase in the dead space during hyperpnoea is due to general relaxation of the bronchial muscular coat, so that air can pass more easily. As, however, the increase occurs without any hyperpnoea, this view becomes untenable: the more so as Professor Dixon informs me that he had meanwhile found in direct experiments on animals that no broncho-dilatation occurs on administering air containing CO_2.[3] It is thus necessary to seek for another explanation.

Considering that the walls of the bronchi are very thick relatively to the walls of the freely distensible air spaces of the surrounding lung-tissue, it does not seem probable that any considerable dilatation of the bronchi can be brought about by mere mechanical distension of the lungs in deep breathing. The position at which the increase of dead space occurs must therefore, I think, be sought beyond the terminal bronchioles. The manner in which a terminal bronchiole in the mammalian lung breaks up was carefully worked out by reconstruction and other methods by W. S. Miller, and is clearly described and figured in his paper.[4] Miller's work seems to furnish the key to the interpretation of the increased dead space. Each terminal bronchus (see fig. 7 and 8 of Miller's paper), ends in several openings or "vestibules," each of which leads into an air-cavity or "atrium," lined

[2] Phil. Trans., B, cciii, p. 221.

[3] The method he used was that employed in the experiments of himself and Ransom on broncho-dilator nerves (Journal of Physiology, xlv, p. 413, 1912). Einthoven observed broncho-constriction under the influence of CO_2 with the vagi intact, and no effect after vagus section. Einthoven, W: Pflüger's Archiv f. d. gesammte Physiologie, 1892, li, pp. 411 and 423.

[4] W. S. Miller, Journal of Morphology, viii, 1893, p. 165.

by alveoli. From each atrium several openings lead onwards into "air-sacs," which are main cavities of which the walls are constituted by alveoli or air-cells. By far the greater number of the lung alveoli belong to the air-sac system, but a very appreciable number belong to the atria, and the latter act partly as air-passages to the air-sacs, and partly perform the same respiratory functions as the air-sacs themselves. The walls of the atria have the same general structure as those of the air-sacs, and must be just as free to expand when air enters the lungs.

It is evident that the atria must have a far greater supply of fresh air than the groups of air-sacs beyond them, since all the fresh air supplied to the air-sacs passes through the atria, and at the end of an inspiration they will be left full of relatively pure air. They will therefore contribute to the "effective" or "virtual" dead space due to the bronchi and upper respiratory passages; and as they will expand freely with a deep inspiration, and be washed out more thoroughly, the dead space will increase with a deep inspiration.

If the lungs as a whole are over-ventilated by temporary forced breathing, the respiratory quotient, as calculated from the composition of the expired air, is extremely high, since over-ventilation extracts much extra CO_2 from the blood, but cannot impart appreciably more oxygen to it. As, however, the atria are, as it were, constantly over-ventilated, the part of the expired air coming from them will have a high respiratory quotient. The air from the air-sacs must therefore have a lower quotient, so that the mixed expired air, coming from atria and air-sacs, has a quotient representing that for the body as a whole. As, moreover, the pulmonary blood passes partly through the atria, though mainly through the air-sacs, the partial pressure of CO_2 in the mixed arterial blood will be slightly lower than that of the blood from the air-sacs, though higher than that of the blood from the atria. This conception explains the fact, noted above, that with very shallow and frequent breathing the excess of CO_2 and deficiency of oxygen in the air-sac air increases.

It is doubtless true that the respiratory exchange of the bronchi and upper air-passages must make some contribution to the total exchange represented in the expired air; but considering the thickness of the bronchial epithelium and the very small mass of the whole mucous membrane lining the bronchi, etc., this contribution must be very small: whereas the extra CO_2 represented by the difference in respiratory quotient between alveolar and expired air represents about 12 per cent of the total CO_2 given off by the body. Moreover it is only during ex-

piration that the bronchial mucous membrane can contribute towards raising the respiratory quotient above that of the alveolar air, since any CO_2 coming off during inspiration is carried down to the alveoli. It seems, therefore, that the respiratory exchange of the bronchial mucous membrane contributes hardly anything to the difference in respiratory quotient between alveolar and mixed expired air. In this conclusion I was confirmed by finding that the respiratory quotient of the first part of the expired air is not strikingly different from that of later parts. The first part would be expected to have a very high respiratory quotient if the respiratory exchange of the bronchi were responsible for the respiratory quotient of the expired air being so much higher than that of the alveolar air.

Priestley and I found that when, during normal breathing, air is expelled sharply from the lungs, the partial pressure of CO_2 in the expired air is constant after a certain amount of air has been expelled, and we inferred that the air of constant CO_2 pressure is alveolar air. It now appears that the air in question is alveolar air from the "air-sacs" of Miller's nomenclature, and that the air from the alveoli of his "atria" is of a different and more variable composition. I have made a few experiments in order to test more definitely than in our original experiments the depth of expiration needed in order to obtain air of constant composition. A rubber bag, of which the capacity when inflated could be varied at will by the adjustment of a large wooden clamp, was attached to the far end of the piece of tubing used for obtaining samples of alveolar air. As the inflation of this bag stopped the expiration, samples of the air leaving the mouth after any desired depth of expiration could be obtained. With ordinary resting breathing (about 18 breaths per minute in my case) the following results were obtained in successive trials on the same day.

DEPTH OF EXPIRATION	PERCENTAGE OF CO_2 IN AIR ISSUING FROM MOUTH	DEPTH OF EXPIRATION	PERCENTAGE OF CO_2 IN AIR ISSUING FROM MOUTH
1350	5.51	650	5.27
190	3.03	650	5.32
335	4.37	650	5.18
510	5.17	1350	5.57
510	4.91	950	5.49
1350	5.39	950	5.53
1350	5.37	1350	5.44
650	4.95	1350	5.63
650	5.23		

If we average this series the results are:

DEPTH OF EXPIRATION	CO_2 PERCENTAGE IN AIR ISSUING FROM MOUTH
190	3.03
335	4.37
510	5.04
650	5.19
950	5.51
1350	5.48

In ordinary determinations of the alveolar CO_2 percentage about 1350 cc. was, so far as I could judge, about the depth of expiration usually employed in my own case. By somewhat forcing the expiration about 1750 cc. could, however, be expired without causing undue delay. A further series (on a different day) was therefore made, to see if any change could be detected in the deepest portions of the expired air. The results were that in six successive determinations the mean percentage of CO_2 was 5.39 with an expiration of 900 cc., and 5.36 with an expiration of 1750 cc. Hence the deeper part of the expiration contained no more CO_2 than the middle part.

A few experiments were also made in order to see what depth of expiration is needed in order to reach a constant CO_2 percentage in a sample taken at the end of inspiration when the breathing was deep. The mean results were as follows, with breathing at a frequency of four per minute, and a depth of about 2000 cc. at 12°.

	DEPTH OF EXPIRATION IN CC. AT 12°	CO_2 PERCENTAGE IN AIR ISSUING FROM THE MOUTH IN A SHARP EXPIRATION AT THE END OF INSPIRATION
First series	460	4.74
	910	5.11
	2550	5.34
Second series	1340	5.10
	2550	5.15

It appears from these results that a depth of expiration of about 1500 cc. would be needed to obtain a sample of undiluted alveolar air

at the end of an inspiration of 2000 cc. With still deeper breathing the depth of expiration needed would doubtless be greater.

If some of the current descriptions of the manner in which the terminal bronchioles are connected with the alveoli were correct it would be hard to offer any explanation of why the composition of the expired air becomes constant after a certain depth of expiration: for according to these descriptions the further away an alveolus is from the terminal bronchus the less fresh air will it receive. Miller's investigations have made it possible to explain the actual facts, including the increase of the virtual dead space with deep breathing.

With regard to methods used for determining the dead space, it seems worthy of remark that the "effective" or "virtual" dead space is a physiological, and not an anatomical conception. The magnitude of this space depends on the physiological efficiency of the respiratory surfaces in relation to the supply of venous blood and fresh air. It therefore seems wrong in principle to use the method of hydrogen inhalation for the purpose of estimating the effective dead space. It is also evident that the varying magnitude of the effective dead space with different depths and types of breathing, and the differences of the dead spaces calculated for oxygen and CO_2, make the calculation of the composition of the alveolar air from that of the expired air a very uncertain matter. In this connection I may perhaps put on record that my own experiments have confirmed the observation of Messrs. Henderson, Chillingworth and Whitney that a pause at the end of inspiration greatly reduces the effective dead space, as would be expected. Increase of depth of breathing must tend to increase the effective dead space, since the atria are more expanded, but increase of frequency must have the same effect, since the air remains for a shorter time in the atria. In very shallow and frequent breathing these two factors appear to counterbalance one another, as seen in the results obtained with a frequency of 60 per minute.

SUMMARY

1. The effective dead space increases enormously with increased depth of breathing, apart from the existence of any hyperpnoea or other causes which might also affect the dead space.

2. This increase is apparently due to mechanical distention of the "atria" into which the terminal bronchioles open.

3. The dead space for oxygen is greater than for CO_2.

4. Estimates of the composition of alveolar air from the composition of the mixed expired air on the assumption of a constant dead space are fallacious.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XXIV. The Tonus and Hunger Contractions of the Stomach of the New-Born

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The gastric hunger mechanism is probably inherited. At any rate, the frequency and duration of the periods of gastric hunger contractions are related to the feeding habits of the individuals or the species only in so far as the feeding time and the food quantity are factors in the time required for emptying of the stomach, and hence for the appearance of the hunger contractions.[1] On the other hand, the hunger mechanism determines to a certain extent the feeding habit. Animals and children probably eat as soon as the stomach is nearly empty, if food is at hand, and the greater frequency of the gastric hunger periods in the young, as shown by Patterson for the dog,[2] is probably related to the more continuous feeding on the part of the young animal.

We have now made observations on a number of new-born infants, and on two pups, born 8–10 days before term, with results showing that the empty stomach at birth and in the prematurely born exhibits the typical periods of tonus and hunger contractions of the adult,[3] the only difference between infant and adult being the greater frequency and relatively greater vigor of these periods in the young. In the case of the two pups, and in some of the infants, the observations were made before their first nursing. It is thus clear that in the normal mammal the gastric hunger mechanism is completed, physiologically, and is probably active some time before birth.

[1] Carlson: This Journal, 1914, xxxiv, p. 169.
[2] Patterson: This Journal, xxxiii, p. 423.
[3] Carlson: This Journal, 1912, xxxi, pp. 151, 175.

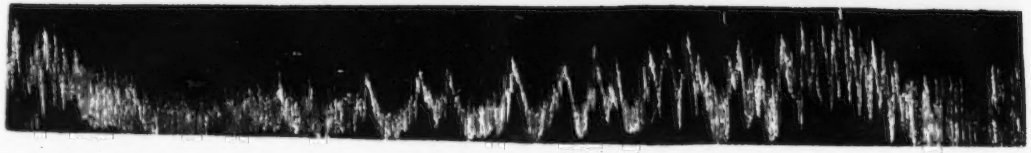

Fig. 1. Tracing showing a period of gastric hunger contractions in a 9-hour old infant, before first nursing. At left end of tracing may be seen the end of the preceding hunger period. Time: 38 minutes. Chloroform manometer.

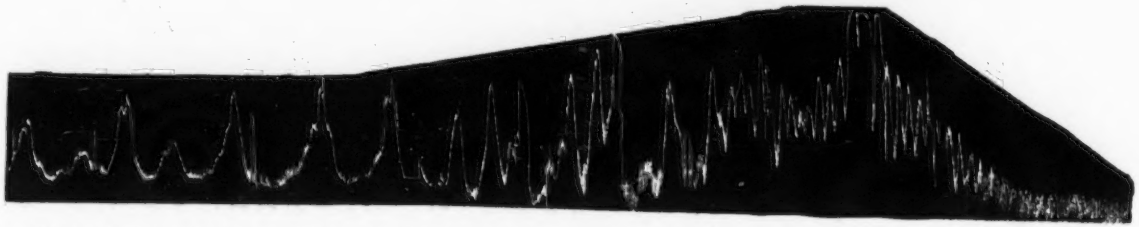

Fig. 2. Tracing showing a period of gastric hunger contractions of a 9-day-old infant, 3 hours after nursing. Note the incomplete tetanus which ends the period. Time: 45 minutes. Chloroform manometer.

The recording of the gastric hunger contractions of the new-born human infant offers no great difficulties. We used delicate rubber balloons of 15 cc. capacity, attached to a flexible rubber catheter of 2 mm. diameter. Most of the infants swallowed this apparatus without difficulty and went to sleep in our arms during the observation periods. The results were always most satisfactory with the infants asleep, as that eliminated all nervous inhibitory factors, and the disturbances from body movements and from irregularities in respiration. Practically nothing can be done with the balloon method if the infant is at all

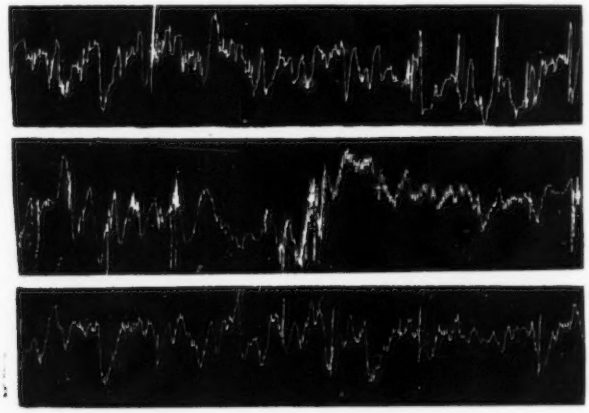

Fig. 3. Tracings of contractions of the empty stomach of a pup born 8–10 days before term. No food given before securing tracings. Time: 10 minutes. Chloroform manometer.

restless. All of our observations were made on healthy and vigorous infants.

The two premature pups were very small, and the balloon introduced into the stomach via the oesophagus had a capacity of only 4 cc.

RESULTS

1. *Human infants.* Periods of gastric tonus and hunger contractions are in evidence shortly after birth and before any food had entered the stomach. These gastric hunger periods exhibit all the peculiarities of the gastric hunger contractions of the adult, except that

the periods of motor quiescence of the stomach between the hunger periods are on the whole much shorter (10–15 minutes). When the gastric hunger contractions become very vigorous the sleeping infant may show some restlessness, and even wake up and cry. If the infant is awake the very vigorous hunger contractions frequently induce crying and restlessness. Two tracings showing typical hunger periods in a nine-hour old infant before first nursing, and in a nine-day-old infant three hours after nursing are reproduced in figures 1 and 2. The reader's attention is called to the fact that in both of these infants the gastric hunger periods end in incomplete tetanus, an index of youth and vigorous stomach.

2. *Prematurely born pups.* The observations were made before any food was given to them. The empty stomach of these very small pups exhibited a continuous motor activity of a character shown in figure 3. These contractions are not identical with the digestion peristalsis, because the latter contractions in the dog occur at 15–18 seconds intervals. The contractions shown in figure 3 last for 30 to 60 seconds or longer, and at times seem to be periods of gastric tetanus. This is the type of motor activity one might expect to observe with the slightly inflated balloon in the cardiac end and the empty stomach in very great tonus.

We are under obligations to Dr. N. S. Heaney of the Presbyterian Hospital for facilities in part of this work. We also wish to thank Mr. I. Tumpowsky and the Misses Jacobson, Rautsche, Clapp, Windmiller, and Jones for their willing assistance.

FACTORS AFFECTING THE COAGULATION TIME OF BLOOD

VII. The Influence of Certain Anesthetics

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In preceding papers of this series evidence was presented that injections of adrenalin result in a hastening of the coagulation time of blood.[1] Other evidence showed that stimulation of the splanchnic nerves produces a like effect upon coagulation time.[2] Several investigators have shown that artificial stimulation of the splanchnic nerves leads to a discharge of adrenalin into the blood.[3] Also it has been proved that certain emotional reactions such as fear and rage occurring in the normal life of an animal induce a discharge of adrenalin. This latter effect has been proved to be due to the passage of impulses along the splanchnic nerves.[4] Elliot has shown that the adrenalin content of the suprarenal glands is reduced by administration of various anesthetics;[5] and that this effect with ether and chloroform is due to stimulation of the suprarenal glands through the splanchnic nerves. A similar result has been shown by another investigator, Oliva.[6] The experiments of the latter showed that chloroform discharges the adrenal glands more completely than does ether. It was also shown in the same experiments that the adrenalin content is more quickly regained after ether anesthesia than after chloroform anesthesia. The question

[1] Cannon and Gray: This Journal, 1914, xxxiv, 232.

[2] Cannon and Mendenhall: This Journal, xxxiv, p. 243.

[3] See Dreyer: This Journal, 1898–99, ii, p. 219; Tscheboksaroff: Archiv fur die gesammte Physiologie, 1910, cxxxvii, p. 103; Asher: Zentralblatt fur Physiologie, 1910, xxiv, p. 927; Kahn: Archiv fur die gesammte Physiologie, 1911, cxl, p. 240; Meltzer and Joseph: This Journal, 1912, xxix, p. xxxiv, 34; Elliott: Journal of Physiology, 1912, xliv, p. 400; Cannon and Lyman: Loc. cit., p. 377.

[4] Cannon and Mendenhall: This Journal, xxxiv, p. 255.

[5] Elliott: Loc. cit., p. 388.

[6] Oliva: Lyon Chirurg., 1914, ii, p. 11.

of the effect of anesthetics upon coagulation time has long been of prime importance to both surgeons and obstetricians. Their chief concern, however, has been in the after-effects as agents productive of post-operative or post-partum hemorrhages. Chloroform seems to be the one most often recognized as causing a change in the coagulation process. Whipple and Hurwitz[7] recently have shown that several hours after administration of large doses of chloroform to dogs the coagulation time is unchanged; they call attention, however, to the weak consistency of the clots. They ascribe the cause of post-operative hemorrhages following administration of chloroform as a failure of the clot to hold firmly rather than a retardation of clotting processes. That the liver is concerned in the coagulation of blood has been shown by many observers.

The foregoing evidence led to the question of the effects of ether and chloroform upon blood coagulation during the administration of the drugs. Inasmuch as experiments recorded in previous papers of this series were concerned with immediate factors affecting coagulation time it was thought logical to study the immediate effects of ether and chloroform upon the coagulation process. These drugs, furthermore, have been shown to exert action upon organs that are intimately involved in blood coagulation, i.e., the liver and adrenals. It was hoped, if changes occurred during anesthesia by these drugs, that such changes might be of value in studying their after-effects or in explaining after-effects of this form of anesthesia upon coagulation time, and also that they might throw some light upon the complex of organs involved in the coagulation mechanism.

The method of drawing blood and recording the coagulation time was the same as described in a previous paper.[8] Decerebrate animals (cats) were used throughout this investigation. Two reasons led to the adoption of this type of animal; first the animals of the whole series were placed under practically uniform conditions, and second, the animal was free from the anesthetic whose action it was desired to study. It was necessary in the beginning of each experiment to induce anesthesia for a short time in order to perform decerebration. Ether was used therefore in the beginning of the experiment. Care was taken to produce not too profound anesthesia and to remove the cerebrum as quickly as possible after beginning the administration of the ether. The usual routine was as follows. Simultaneously with secur-

[7] Whipple and Hurwitz: Journal of Experimental Medicine, 1911, xiii, p. 136.
[8] Cannon and Mendenhall: This Journal, xxxiv, p. 225.

ing the animal on the board the ether was applied with a cone, and the neck was prepared by clipping the hairs. By this time anesthesia was deep enough to permit operative procedures. The animal was then tracheotomized, a tracheal cannula inserted, and both carotids tied. Then it was turned over and decerebration performed according to the method described recently by Forbes and Sherrington.[9] The total time elapsing from the application of ether to its removal never exceeded fifteen minutes, usually it was from ten to twelve minutes. After decerebration the femoral artery was prepared according to directions given in a preceding paper of this series.[10] The temperature of the animal was maintained when necessary by an electric heating pad. A thermometer was inserted into the rectum. The ether or chloroform was given by means of the bottle used in ordinary laboratory operations. It consisted of a small bottle of about 75 cc. capacity. It was stoppered by a rubber cork through which passed two right angle glass tubes, each 1 cm. in diameter. One of these tubes conducted air to the surface of the anesthetic; the other conducted the ether-air mixture to the animal by means of a short rubber tube connected to the tracheal cannula. This rubber tube had an oblique cut in the wall so that by shifting the bottle more air could be mixed with the ether if the animal showed signs of asphyxia. The corneal reflex was used to determine if anesthesia was present; also vibrissae, ear and tail reflexes were used. After all operative procedures were finished the animal was left undisturbed for forty-five minutes or an hour. This was done in order that the animal might be free from ether when observations were to be made, and also because of the discovery recorded in a previous paper that operative procedures may shorten the coagulation time. It was felt that the time mentioned above sufficed to free the animal from the preliminary small dose of ether and also any hastening factor that may have been aroused by operations. All experiments began with observations taken at intervals of ten minutes for forty minutes or an hour to determine the normal coagulation time of the animal, then anesthesia was induced by the means described above and observations continued every ten minutes for an hour.

A total of sixty-three successful experiments were performed. Preliminary to the investigation of chloroform a number of experiments were made with chloral hydrate. It was thought that this drug would give some valuable data which would be indicative of the action of the

[9] Forbes and Sherrington: This Journal, 1914, xxxv, p. 367.

[10] Cannon and Mendenhall: Loc. cit., p. 227.

whole series of chlorine containing anesthetics. Moreover it might reduce the number of animals which would be necessary for the study of chloroform. Thus the fatalities resulting from the powerful toxicity of the chloroform would be reduced. In actual practice, however, the fatalities due to chloroform were surprisingly small. Inasmuch as chloral hydrate is frequently used for its anesthetic effect, the study of its influence upon coagulation is not without value.

TABLE 1

Effect of chloral hydrate

EXPERIMENT NO.	DAYS IN STOCK	SEX	DOSE IN MGMS. PER KILO	NORMAL COAGULATION TIME	PER CENT INCREASE COAG. TIME	PER CENT DECREASE COAG. TIME
1	120	Female	90	2.4	50.0	
5	¼	Male	65	2.8	60.0	
4	4	Male	65	2.8	142.0	
2	4	Female	65	3.6	30.5	
3	2	Female	65	4.0	5.0	
38	3	Male	70	6.4	10.9	
39	4	Male	70	6.5	15.3	
8	4	Female	100	6.8	0.0	0.0
42	½	Female	70	6.8	20.5	
7	3	Male	100	6.9		8.7
6	3	Male	100	7.0		7.0
41	1	Female	70	7.7		20.7
40	3	Male	80	7.9		6.3
31	2	Female	100	8.0		13.7
44	3	Female	70	8.6		6.9
43	0	Male	70	9.3		7.5
45	0	Female	80	9.3		11.8
Average				6.2	37.1	10.3

Effect of chloral hydrate. A total of twenty-three experiments were performed with chloral. Table 1 shows the results of seventeen of these experiments arranged in ascending order according to length of the normal coagulation time. The increase or decrease of coagulation time is represented in per cent of the normal. The doses were given intravenously. Injection was made slowly. It usually took three to five minutes to introduce the drug. The dose varied from 65 to 100 mgm. per kilogram. Six experiments were performed with large toxic doses (150–165 mgm. per kilogram). These are not included in the table because they are of no interest except from a toxi-

cological standpoint. Three of them showed an increase, one no change, and two a decrease in coagulation time. A glance at the table reveals the curious fact that the effect which chloral hydrate has upon coagulation bears a distinct relation to the coagulation time before chloral was administered. It is noted that if the normal coagulation time of the blood was 6.8 minutes or less, chloral prolonged the coagulation; whereas, if the normal coagulation time was 6.9 minutes or more, then chloral decreased the coagulation time. That this effect is not due to size of dosage is revealed by the table; furthermore it is unlikely that it may depend upon the sex of the animal or the length of time it had been in stock. Thus Experiment 42 was a female in stock one-half day and received a dose of 70 mgm. per kilogram. Its normal coagulation time was 6.8 minutes. Chloral increased the coagulation

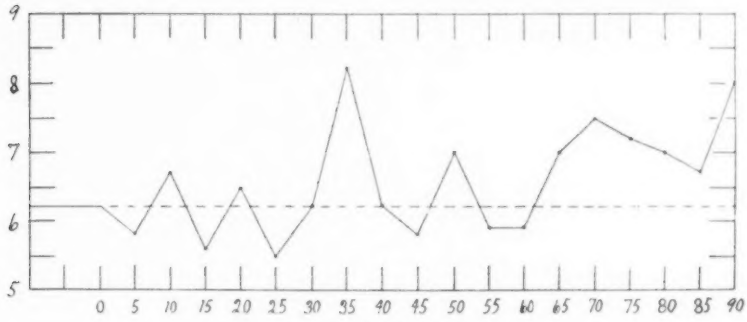

Fig. 1. Effect of chloral hydrate.

time 20.5 per cent. Experiment 41 was a female in stock one day; it received the same dose per kilogram; its normal coagulation time was 7.7 minutes. Chloral in this instance decreased the coagulation time 20.7 per cent. This shows clearly that sex and size of dosage are not the determining factors in the effect of chloral hydrate upon coagulation time. A point of further interest in the above two experiments was in the weights of the animals. It was a mere coincidence that their weights were exactly the same 2.6 kgm., and therefore each received the same size of dose of chloral. Figure 1 is a composite curve based upon the results obtained in Table 1. The straight line at the beginning of the curve represents the average normal coagulation time. It is extended as a line of dashes through the length of the curve. The ordinates represent minutes of time for coagulation to occur. The

abscissae represent intervals of five minutes from the time when the drug was given. The general averages of these experiments showed a normal coagulation time of 6.2 minutes. After chloral was administered the average coagulation time increased 4.8 per cent. Figure 2 is a composite curve constructed in the same manner as the one above. In this curve only those experiments were used whose normal coagulation time was 6.8 minutes or less. It is noted that only once did the coagulation fall below the normal, and then only 0.1 minute. The curve shows the striking effect that chloral hydrate has upon a short coagulation time. The average increase in coagulation time as shown by this curve amounted to 28.2 per cent. Figure 3 is a curve which is composed of those experiments whose normal coagulation was de-

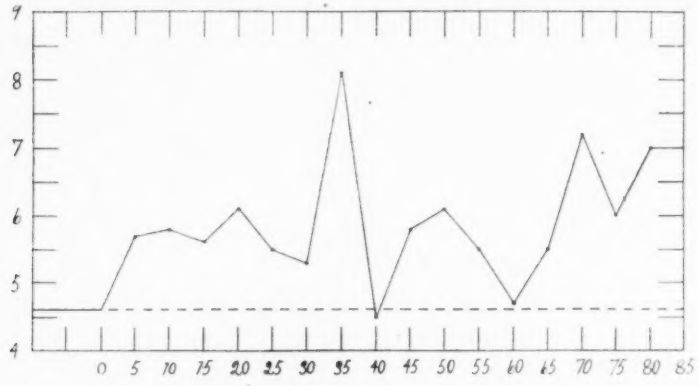

Fig. 2. Effect of chloral hydrate (short normal).

creased in these observations. The average decrease amounts to 7.5 per cent. The decrease does not correspond to the increase. In the first paper of this series the per cent of average error due to the method is stated as 6 per cent. Therefore, the result when the normal coagulation time was long might be regarded as nil. The fact that chloral hydrate exerts its retarding effect more when a short normal is present suggests the idea that it acts antagonistically to hastening factors present in the blood or that it may depress activity of organs which produce or activate hastening factors. The action of chloral hydrate upon the liver is too well known to need description here. There seems to be no reference available in regard to its effect upon the adrenals. If chloral hydrate caused the production of factors that retarded coagula-

tion one should expect it to exert its retarding effect even though the normal coagulation was long. Only one clear instance of this is shown and then a large toxic dose of chloral hydrate was used. Thus in Experiment 36 the average coagulation time for a half hour preceding the injection of chloral hydrate was 8.8 minutes; for forty minutes following the injection the average was 9.6 minutes, an increase of 9.0 per cent. This result is not far from the average per cent of error. Experiment 32 was another (normal 8.0 minutes) in which a toxic dose of the drug was used. This showed an increase of 16 per cent over the normal. The evidence in this experiment was not clear, inasmuch as the animal became extremely irritable after decerebration and because of twitching made difficult the drawing of blood. The

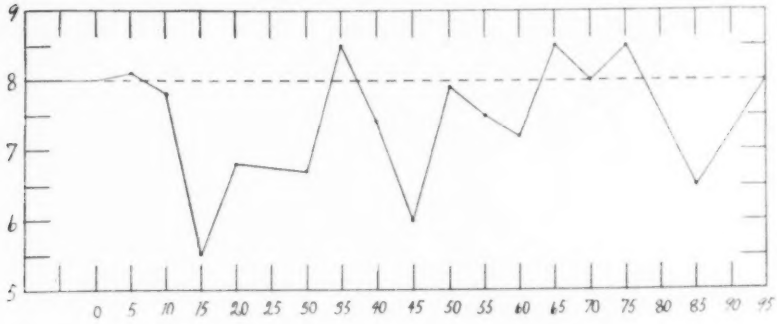

Fig. 3. Effect of chloral hydrate (long normal).

general disturbance present in this animal made the normal coagulation time doubtful. The animal became quiet after the chloral was injected. Experiment 33 was another instance in which a long normal (10.2 minutes) was increased by a toxic dose of chloral hydrate. Here again the evidence is not clear, because the animal had just come into the laboratory and in observations lasting an hour before chloral was given the coagulation time fluctuated from 6.5 minutes to 14.5 minutes. After chloral was given the respiratory center was paralyzed and artificial respiration became necessary. The increase amounted to 13.7 per cent. Contrary to this experiment is one (Exp. 37), in which a toxic dose was given to an animal whose coagulation time was short (6.0 min.). Here there was practically no change whatever. This was a male animal, in stock two days. It fought furiously while being placed upon the board and continued thus until anesthesia be-

came effective. Experiment 8 is an example of a short coagulation remaining unchanged, but the dose was not toxic. This animal, a female, had been in stock four days. The weight of evidence obtained in these experiments shows that chloral hydrate, if it affects the coagulation at all tends to prolong it. The prolongation is greatest when the normal coagulation is short. The evidence does not warrant a conclusion that retarding factors are produced.

Effect of chloroform. Fifteen experiments were performed with chloroform. Table 2 shows the results obtained. The amount of chloroform used varied somewhat, the average being 10 cc. Anesthesia, as noted by reflexes, was usually complete in from three to four minutes. With two exceptions, Experiments 58 and 50, chloroform behaved

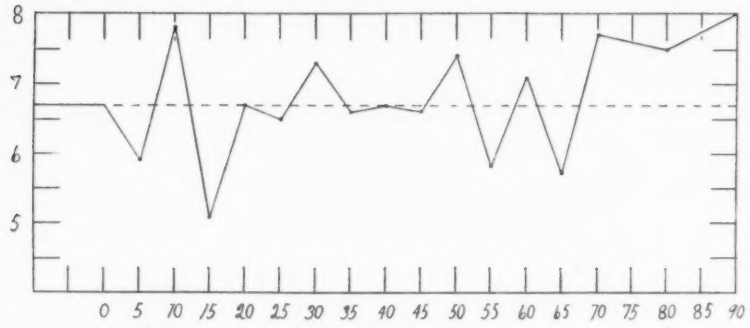

Fig. 4. Effect of chloroform.

similarly to chloral hydrate—thus if the normal coagulation time was short chloroform prolonged it, whereas, if it was long a decrease resulted. In these experiments as in those with chloral hydrate a composite curve shows little effect of the drug upon coagulation time other than to make it irregular. Figure 4 is such a curve constructed upon the basis of the observations in Table 2. The average normal coagulation time in this set of experiments with chloroform was 6.7 minutes. The average coagulation time during administration of chloroform was the same, 6.7 minutes; hence the change in per cent was 0.0. This, however, was a mere coincidence, since leaving out any one experiment would alter the figures slightly one way or the other. A curious fact is noted in the point where chloroform action changes from an increase to a decrease of coagulation time. It occurs at 7.5 minutes. With chloral hydrate it was 6.8 minutes, a difference of less than a minute.

TABLE 2

Effect of chloroform

EXPERIMENT NO.	DAYS IN STOCK	SEX	NORMAL COAGULATION TIME	PER CENT INCREASE COAG. TIME	PER CENT DECREASE COAG. TIME
52	2	Male	4.7	10.6	
63	1	Male	5.3	9.4	
58	3	Female	5.5		3.6
50	1	Female	5.8		1.7
56	2	Male	6.0	25.0	
54	1	Female	6.2	8.0	
51	2	Male	6.4	3.1	
53	3	Male	6.6	16.6	
57	1	Male	6.6	18.1	
59	3	Male	7.1	2.8	
55	2	Female	7.5	2.6	
62	1	Female	8.0		18.7
61	3	Female	8.5		8.2
60	4	Male	9.0		5.5
46	½	Male	9.2		8.6
Average			6.7	10.6	7.7

Figure 5 is a curve constructed from observations made in those experiments in which the normal coagulation time was 7.5 minutes or less.

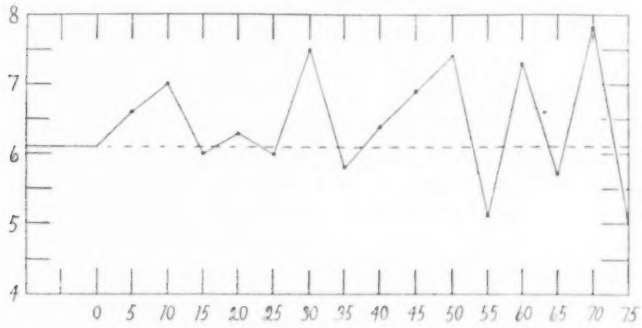

Fig. 5. Effect of chloroform (short normal).

The average normal coagulation time in these experiments was 6.1 minutes. After the chloroform was given there was an increase of 4.9 per cent. Figure 6 is a curve in which the normal coagulation time was

over 7.5 minutes. The average normal was 8.6 minutes. After the chloroform was given it decreased 11.6 per cent. The increase in coagulation time when the normal was short was not as pronounced as in the chloral hydrate experiments. In figure 5, however, there were included two experiments in which there was a decrease in coagulation time. If the average decrease is calculated in all experiments that show a decrease it is found to be 7.7 per cent; whereas, if the average increase is estimated, it is found to be 10.6 per cent. Moreover the average short coagulation normal with chloral hydrate was 4.6 minutes, while with chloroform it was 6.1 minutes. Chloroform is known to affect two organs that are important in coagulation processes, i.e.,

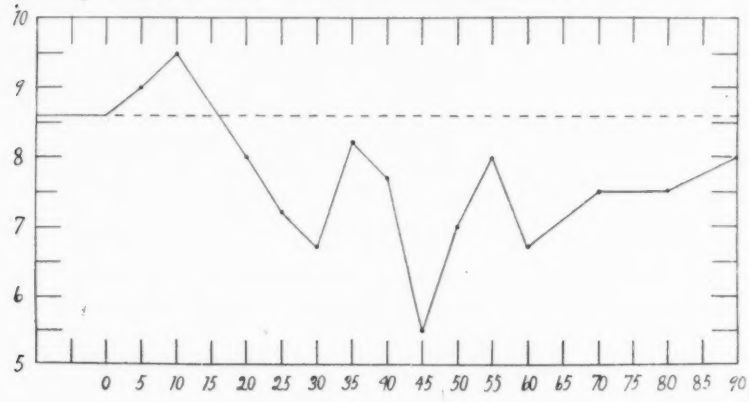

Fig. 6. Effect of chloroform (long normal).

the liver and the adrenals. It would be natural to suppose that its effect at any one time upon coagulation would depend upon various interrelations among many factors. If the adrenals were discharged completely it might still exert an effect upon coagulation by disturbance of liver function; or if the adrenals were highly charged, the resulting outpour might or might not be effective because of an impairment of liver function. The following protocol is typical of cases of chloroform anesthesia in which coagulation was prolonged.

Protocol Experiment 54.

February 10, 1915. Female cat, in stock 1 day, weight 2.5 kgm.
1.05 Placed on board and anesthetic (ether) begun.
1.15 Tracheal cannula placed and carotids tied.

1.20 Decerebration completed, ether removed.
1.40 All operative procedures completed.
2.45 Coagulation time 6.0 minutes.
2.55 Coagulation time 6.5 minutes.
3.05 Coagulation time 5.5 minutes.
3.15 Coagulation time 6.5 minutes.
3.25 Coagulation time 6.5 minutes.

Average 6.2

3.35 Chloroform administered
3.45 Coagulation time 6.0 minutes.
3.55 Coagulation time 7.0 minutes.
4.05 Coagulation time 6.0 minutes.
4.15 Coagulation time 5.0 minutes.
4.25 Coagulation time 8.0 minutes.
4.35 Coagulation time 8.5 minutes.

Average 6.7

4.36 Chloroform removed
4.45 Coagulation time 8.5 minutes.
4.55 Coagulation time 6.0 minutes.
Temperature variation in animal 1° C.
Water bath constant 25° C.

Figure 7 gives a summary of this experiment. In this experiment the increase amounts to 8.0 per cent, but the curve is typical of the increase shown by chloroform, i.e., the increase is more noticeable about an hour after the beginning of the anesthetic. Previous to the increase there may be evidence of a disturbance of balance between opposing forces with a final predominance of the factors that retard coagulation or perhaps a decrease in effectiveness of hastening factors. After the chloroform is removed the hastening factor again appears. The following protocol is of interest because of the opposite effect that is shown.

Protocol Experiment 61.

March 1, 1915. Female cat, in stock 3 days, weight 3.2 kgm.
1.10 Animal placed on board and etherization begun.
1.20 Tracheal cannula placed and carotids tied.
1.25 Decerebration completed, ether removed.
2.10 All operative procedures completed.
3.15 Coagulation time 8.5 minutes.
3.25 Coagulation time 8.5 minutes.
3.35 Coagulation time 8.5 minutes.

Average 8.5

3.36	Chloroform administered	
3.45	Coagulation time	10.0 minutes.
4.00	Coagulation time	8.0 minutes.
4.10	Coagulation time	7.5 minutes.
4.20	Coagulation time	5.5 minutes.
		Average 7.8
4.21	Chloroform removed	
5.40	Coagulation time	10.0 minutes.
Temperature variation in animal		2.5° C.
Temperature water bath constant		25° C.

The experiment is summarized in figure 8. In this experiment the average normal was 8.5 minutes. Forty-five minutes following the introduction of chloroform the coagulation time was shortened 35.2 per cent. One hour and forty minutes after chloroform was removed the coagulation time had increased over 50 per cent. The average coagulation time throughout the whole forty-five minutes of chloroform anesthesia showed a decrease of only 8.2 per cent. The evidence obtained in these experiments with chloroform shows a marked resemblance to that obtained with chloral hydrate. If the coagulation time is affected at all it is usually retarded, except when the normai coagulation time is long, when it may be decreased. The evidence does not indicate that retarding factors are produced.

Effect of ether. A total of 21 experiments were performed with ether. Thirteen were made with adrenals intact and eight with adrenals removed. Table 3 shows the results obtained in the experiments in which the adrenals were intact. In no instance did ether increase the coagulation time. An average of 50 cc. of ether was used in each experiment. The percentage decrease in coagulation time varied from 0–24 per cent. Figure 9 is a composite curve based upon the observations obtained in Table 3. The normal coagulation time was 7.2 minutes. Ether decreased it 15.2 per cent. There was no distinct relation between normal coagulation time and the effect of ether. The longest normal was 9.4 minutes; this was decreased 11.7 per cent; the shortest normal was 5.6 minutes; it was decreased 24.4 per cent. Experiments 16, 17, and 22 showed practically no change, but these may readily be explained. In Experiment 16 the animal had been in stock only 12 hours. During the first 35 minutes of ether anesthesia the coagulation time increased, reaching 37.0 per cent above the normal; twenty-five minutes later the coagulation time was 19.3 per cent shorter than normal. It continued with some variation for over an hour.

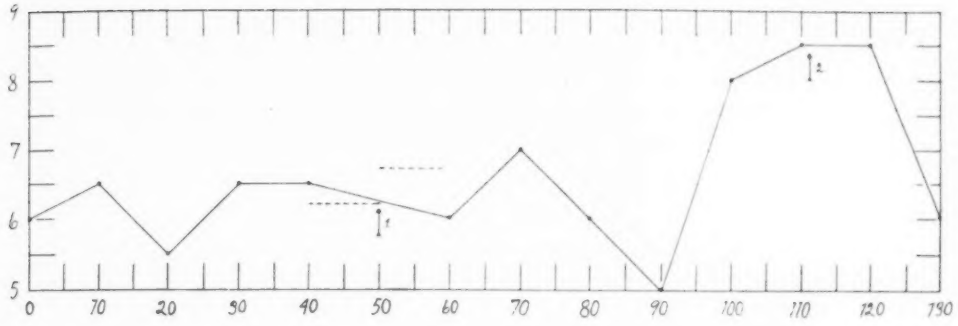

Fig. 7. A summary of Experiment 54. Chloroform was given at 1, removed at 2. Dotted lines represent averages of coagulation time before and after chloroform was given.

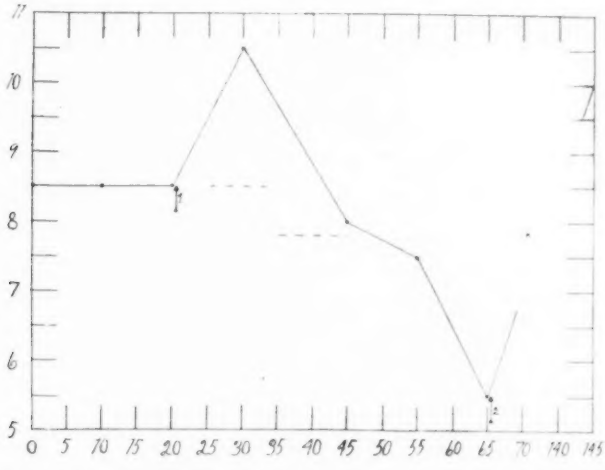

Fig. 8. Summary of Experiment 61. Chloroform given at 1, removed at 2. Dotted lines represent averages before and after chloroform was given.

This caused the final average to appear the same as the normal, when the real effect was a marked diminution. Experiment 17 showed a similar initial rise followed by a drop in the coagulation time. The animal had been in stock 20 hours. In Experiment 22 the animal died suddenly one hour after the ether was started. The coagulation time was irregular throughout the experiment. The following protocol is typical of the ether effect.

TABLE 3

Effect of ether (adrenals intact)

EXPERIMENT NO.	DAYS IN STOCK	SEX	NORMAL COAGULATION TIME	PER CENT INCREASE COAG. TIME	PER CENT DECREASE COAG. TIME
19	3	Male	5.6		24.4
14	2	Female	6.1		9.8
16	½	Male	6.2		
17	¾	Male	6.3		3.1
21	1	Female	6.5		7.6
12	150	Female	6.8		13.2
13	150	Female	6.8		17.6
11	150	Female	7.1		23.9
18	2	Female	7.6		21.0
15	2	Female	8.5		15.3
22	2	Female	8.8		1.1
20	6	Male	9.1		8.7
10	?	Male	9.4		11.7
Average			7.2	0.0	15.2

Protocol Experiment 15.

November 11, 1914. Animal in stock 2 days, female, weight 2.4 kgm.

1.50 Animal placed on board, etherization begun.
1.55 Tracheal cannula placed and carotids tied.
2.00 Decerebration completed, ether removed.
2.15 Operations completed.
3.00 Coagulation time 7.5 minutes.
3.10 Coagulation time 8.0 minutes.
3.20 Coagulation time 10.0 minutes.
3.35 Coagulation time 8.5 minutes.
3.45 Coagulation time 8.5 minutes.
3.55 Coagulation time 8.5 minutes.

Average 8.5

4.00 Ether
4.05 Coagulation time 9.5 minutes.
4.15 Coagulation time 6.5 minutes.
4.25 Coagulation time 7.0 minutes.
4.35 Coagulation time 8.5 minutes.
4.45 Coagulation time 6.5 minutes.
4.55 Coagulation time 6.5 minutes.
5.05 Coagulation time 7.0 minutes.
5.15 Coagulation time 6.5 minutes.

Average 7.2

Animal's temperature showed variation of 1.0° C.
Temperature of water bath constant 25° C.

TABLE 4

Effect of ether (adrenals removed)

EXPERIMENT NO.	DAYS IN STOCK	SEX	NORMAL COAGULATION TIME	PER CENT INCREASE COAGULATION TIME	PER CENT DECREASE COAGULATION TIME
25	4	Male	5.9	13.5	
24	3	Female	6.9		2.8
29	0	Male	7.2		3.7
28	2	Male	7.3		8.2
27	5	Male	7.3		
30	5	Female	7.9		1.2
23	3	Male	8.7		6.8
26	0	Male	9.3		7.5
Average			7.5		1.3

Figure 10 shows a summary of the experiment.

The consistent action of ether suggested the idea that only one factor of coagulation, the hastening factor, was affected. Since Elliott has shown that ether discharges the adrenal gland it was thought desirable to remove the adrenals and see if adrenalin was the factor which was affected. Table 4 shows the results of 8 experiments with adrenals removed. The results are interesting in that one shows an increase of 13.5 per cent. This was the only experiment with ether that showed an increased coagulation time. The remaining experiments all showed a decrease, but the decrease was so slight that it was practically nil. All might easily fall within the range of per cent of error. Figure 11 is a composite curve based upon observations recorded in Table 4. The effect of removal of adrenals is clearly shown by comparing this

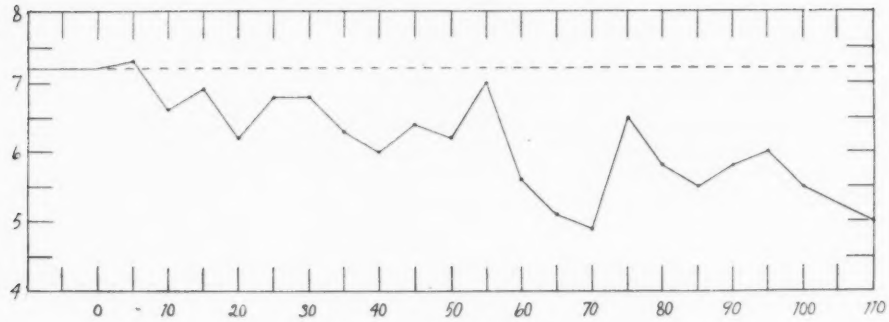

Fig. 9. Effect of ether (adrenals intact).

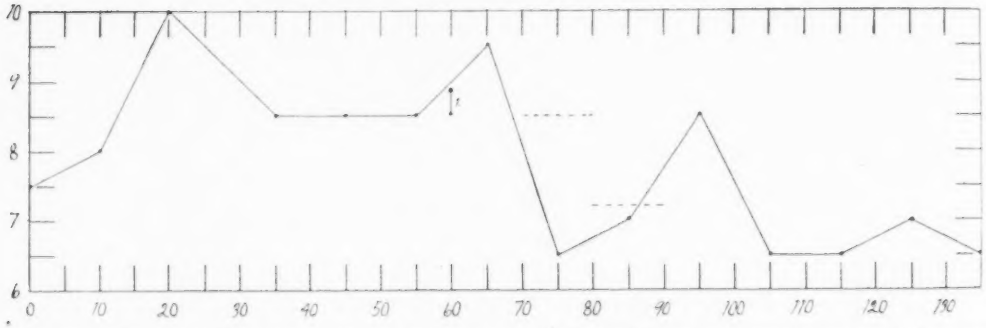

Fig. 10. Summary of Experiment 15. Ether given at 1. Dotted lines represent averages before and after ether was given.

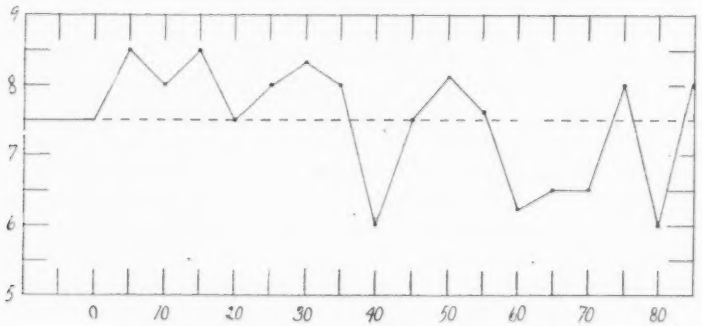

Fig. 11. Effect of ether (adrenals removed).

curve with figure 9 where the adrenals are intact. The average decrease per cent with adrenals out was 1.3 per cent. The evidence shows therefore that ether decreases the coagulation time and that the effect is exerted through the adrenal glands.

Since the experiments with chloral hydrate and chloroform show so much irregularity it is conceivable that more than one organ is involved by them in the coagulation changes. That both drugs affect the liver is well known and that chloroform discharges the adrenal glands has been described by two investigators. The action of chloral hydrate upon coagulation time points to involvement of a hastening and a retarding process. Possibly the adrenals are discharged by chloral hydrate, just as they are by chloroform. It was not shown in these experiments that chloral hydrate or chloroform produces or stimulates the production of a factor retarding coagulation. The experiments in which increase in coagulation time was shown might well be explained in another way. For example, in Experiment 37 mentioned above, the normal coagulation was 6.0 minutes. A toxic dose of chloral hydrate produced practically no change in the coagulation time. This seems to add additional evidence to support the suggestion made in a previous paper that a hastening process may involve the action of a factor upon the liver (or intestine).[11] It may readily be conceived here that chloral hydrate discharged the adrenal gland, and at the same time rendered the liver incapable of being acted upon by the adrenal secretion. As a result no hastening of coagulation occurred. The animal in this experiment was a male in stock two days and had fought vigorously. He might easily have largely discharged his adrenal glands so that no more was discharged by chloral hydrate. This would have left chloral hydrate free to stimulate at least temporarily the production of a retarding factor if it had such power. The evidence, however, is negative. Thus the coagulation time before the introduction of chloral hydrate was as follows: 6.0, 5.5, 5.5; afterward it was 6.0, 5.5, 6.5, 5.5, 6.0. The actions of chloroform, which is known to discharge adrenalin (a hastening factor), may well be explained in terms of the factor of adrenalin and its action upon a susceptible or non-susceptible liver. Chloroform showed usually a retarding influence upon coagulation. This may have been due to its action upon the liver. Thus it may stop the action of adrenalin upon the liver and in that way remove the factor that was keeping the coagulation time

[11] Cannon and Mendenhall: Loc. cit., p. 250.

low. In figure 7 above it is seen that the prolongation did not occur until several minutes after the chloroform was given. Ten minutes after the chloroform was removed the coagulation process was still prolonged, but in the following ten minutes it returned to normal. This may be explained by the liver again becoming susceptible to the action of adrenalin. The decrease in coagulation shown by chloroform may be explained in terms of the adrenalin factor also. Thus in figure 8 above, the animal had been in stock three days, had become quiet, and naturally the hastening factor, adrenalin, was not being discharged. Its coagulation time was consequently long, 8.5 minutes. It has been shown that a *large* amount of adrenalin may produce first a retardation and then an acceleration of coagulation.[12] The first

TABLE 5

Summary of data

TOTAL NO. EXPERIMENTS	NORMAL COAGULATION TIME	DRUG	PER CENT INCREASE COAGULATION TIME	PER CENT DECREASE COAGULATION TIME
17	6.2	Chloral hydrate	4.8	
9	4.6	Chloral hydrate	28.2	
8	8.0	Chloral hydrate		7.5
15	6.7	Chloroform		
11	6.1	Chloroform	4.9	
4	8.6	Chloroform		11.6
13	7.2	Ether (adrenals intact)		15.2
8	7.5	Ether (adrenals removed)		1.3

application of chloroform may have discharged an amount of adrenalin which acted upon the liver and produced the *retarding* factors before the liver became insusceptible to the action of adrenalin. As the chloroform was administered it continued to discharge adrenalin and when it was removed and the liver again became susceptible to its action it acted the same as a large dose of adrenalin at any time. It prolonged the coagulation time.

The evidence with ether points clearly toward involvement of one factor of coagulation, adrenalin. It might be regarded as a bloodless method of injecting adrenalin intravenously. Thus in Experiment 16 above the preliminary rise is typical of a large dose of adrenalin and

[12] Cannon and Gray: Loc. cit., p. 238.

the subsequent fall is typical. Experiment 17 is a similar effect. This preliminary rise frequently caused the final average to appear smaller than it actually was. That adrenalin is the factor involved is shown in the experiments in which the adrenals were removed. That most of them still showed a decrease may easily be due to discharge from accessory chromaffin tissues. Some control experiments in which nothing was given showed that the coagulation time decreased slightly as the experiment proceeded. No explanation is offered for the one instance in which ether prolonged the coagulation time when the adrenals were excluded. Table 5 shows briefly the results obtained in all the experiments.

SUMMARY.

The observations in these experiments seem to warrant the following conclusions.

1. Coagulation time is little altered by chloral hydrate unless it is normally short, then it is prolonged.

2. Coagulation time is affected by chloroform as by chloral hydrate, i.e., if the process is affected at all it more usually is prolonged rather than hastened.

3. The effects of chloral hydrate and chloroform are probably the result of disturbance and consequent interaction between two or more organs which are important in the coagulation process; probably liver (intestine?) and adrenal glands.

4. The evidence is not sufficient to prove that a retarding agent is produced.

5. Coagulation processes are hastened by ether anesthesia.

6. The effect of ether is exerted wholly through its action upon the adrenals.

A CALORIMETRIC CALIBRATION OF THE KROGH BICYCLE ERGOMETER

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Contribution from the Nutrition Laboratory of the Carnegie Institution of Washington, Boston, Mass.

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A quantitative study of the relation between muscular work and total metabolism requires the use of some form of apparatus which will transform the muscular work into measurable units. In a considerable part of the earlier research on this problem with man, the arms have been employed to rotate ergometers of various forms. Much valuable research has been carried out by Zuntz and his associates with a piece of gymnasium apparatus designated by them as the Gaertner ergostat, with the brake ergometer of Zuntz,[1] and with the dynamometer of Fick.[2] Johansson, Tigerstedt, and their associates have also made studies with Johansson's extraordinarily ingenious ergostat.[3]

In recent years the use of some form of bicycle has been recognized as affording the most practical method for securing large amounts of external muscular work and at the same time obtaining a relative fixation of the body of the subject, so as to permit the measurement of the gaseous metabolism by some type of breathing appliance. One of the earliest uses of the bicycle form of ergometer was that made by Atwater and Benedict[4] in which a small pulley attached to the armature shaft of a generator pressed against the rear wheel of a stationary bicycle. When the subject was pedaling, the friction between the wheel and the pulley developed an electric current in the armature which could be measured. Subsequently a special type of bicycle ergometer was devised on the electric brake principle, which was used in a series of investigations with the respiration calorimeter at Wesleyan University,

[1] Zuntz: Archiv für Physiologie, 1899, p. 372.

[2] Fick: Archiv für die gesammte Physiologie, 1891, l, p. 189.

[3] Johansson: Skandinavisches Archiv für Physiologie, 1901, xi, p. 273.

[4] Atwater and Benedict: U. S. Department of Agriculture, Office of Experiment Stations, Bulletin 109, 1902, p. 20.

Middletown, Connecticut, in studying the effective work produced by several bicycle riders. The apparatus was briefly described in a publication by Benedict and Carpenter;[5] more recently a detailed description of the apparatus, together with a series of interesting calorimetric calibrations made with it, was published by Benedict and Cady.[6]

Bowen[7] published in 1903 a description of an ergometer in which the rear wheel of a bicycle was replaced by a grindstone, weighing about 50 kilograms, the apparatus being also supplied with a brake. Later some researches made with this ergometer were published.[8]

As a means for securing a considerable amount of muscular work, Haldane fitted up a tricycle, weighting the wheels heavily to convert them into fly wheels, and using a brake consisting of a strap passed around the brake-wheel. The records were made on a spring balance.[9]

Zuntz exhibited an apparatus at the Dresden Hygiene Congress in 1911 in which a brake was applied to a bicycle ergometer fashioned much after the design of the Zuntz brake ergometer. To our knowledge no description of this apparatus has thus far been published. Personal inspection of it by one of us showed that it is very well constructed and should give most satisfactory results.

Amar also used a bicycle, the rear wheel being supplied with a special weight attached with a broad steel band. He adapted a brake to the instrument and connected it with either a dial dynamometer or a balance.[10]

Boussaguet likewise used a bicycle, fitted with a Prony brake, in studying the work of miners.[11]

More recently Martin[12] has described a simple and convenient form of bicycle ergometer, maintaining that the instrument has an error of less than 1.0 per cent. A special cast iron wheel is used in place

[5] Benedict and Carpenter: U. S. Department of Agriculture, Office of Experiment Stations, Bulletin 208, 1909, p. 11.

[6] Benedict and Cady: Carnegie Institution of Washington Publication No. 167, 1912; Cady and Benedict: Physikalische Zeitschrift, 1912, xiii, p. 920.

[7] Bowen: Contributions to Medical Research dedicated to Victor Clarence Vaughan, June, 1903, p. 462.

[8] Higley and Bowen: This Journal, 1904, xii, p. 311.

[9] Haldane: Journal of Physiology, 1905, xxxii, p. 225.

[10] Amar: Le rendement de la machine humaine, Paris, 1910, p. 30; Journal de Physiologie et de Pathologie générale, xiv, p. 298, 1912; Le moteur humain, Paris, 1914, p. 390.

[11] Boussaguet: Recherches expérimentales sur les conditions physiologiques du travail des mineurs. Thèse, Paris, 1912.

[12] Martin: Journal of Physiology, 1914, xlviii, p. xv.

of the rear wheel of the bicycle; a fabric band is wrapped around this wheel and connected with two spring balances which indicate the amount of tension. As yet we have seen no publication of researches carried out with this ergometer.

Finally Krogh[13] of Copenhagen has modified and greatly improved the electric brake bicycle ergometer. He has most ingeniously applied the electric brake principle and has also been able to weigh the work done with the apparatus. Krogh's instrument, which was first exhibited at the International Congress in Groningen, appeared to be so well adapted for quantitative studies of the relation between muscular work and metabolism that it was secured for the Nutrition Laboratory.

With all forms of electric brake apparatus there is always an element of uncertainty as to the variations in the mechanical friction with load. Furthermore, there is always present the possibility of the distortion of the magnetic field as a result of the rotation of the copper disk. With the original form of ergometer it was observed that there was a most singular calibration curve and that the amount of work done was not directly proportional to the number of revolutions, since the heat per revolution varied considerably with different speeds. The wholly unexpected calibration curves found by Benedict and Cady[14] have made all who attempt to work with this type of apparatus somewhat uncertain as to the exact values to be obtained at different speeds. Theoretically, the electric brake ergometer of Krogh eliminates in large part all of the errors incidental to the earlier form of the bicycle ergometer; nevertheless it seemed necessary to calibrate the new instrument carefully, preferably in heat units.

When an attempt was made to calibrate the first electric brake ergometer, it was suggested by Professor Atwater that the instrument be placed inside of the respiration calorimeter and rotated by means of a shaft and motor outside of the calorimeter chamber. The amount of heat generated per revolution could then be directly determined by the calorimeter. This method of calibration proved most satisfactory and a series of tests made with the calorimeter at Middletown and a few years later with the chair calorimeter in the Nutrition Laboratory showed a remarkably close agreement.

Since ultimately in metabolism studies a knowledge of the calories resulting from muscular work is particularly desired, the measurement

[13] Krogh: Skandinavisches Archiv für Physiologie, 1913, xxx, p. 375.
[14] Benedict and Cady: loc. cit.

in heat units of the work done has distinct advantages. Furthermore such a method of calibration takes into account all errors due to friction which cannot be estimated by ordinary methods. The friction tests with the first form of ergometer showed that in all probability, with a well constructed bicycle, using sprocket wheels and roller bearing chains, the friction was practically negligible. Nevertheless, the uncertainty as to the exact values obtained with the ergometer is well pointed out by Krogh in discussing the sources of error in the apparatus. After conference with Dr. Krogh it was decided that the instrument would probably prove of such general application for muscular work experiments that its calibration in one of the respiration calorimeters of the Nutrition Laboratory would be highly desirable. Accordingly we mounted the apparatus in a large calorimeter and have made a series of tests with it which are described in this paper.

The Krogh ergometer consists of an ordinary bicycle from which the front wheel is removed. The rear wheel is replaced by a copper disk having a lead ring around the periphery, this weighted wheel acting more or less as a fly wheel. The four magnets, instead of being mounted permanently as in the original bicycle ergometer, are mounted on a metal frame which is attached with ball bearings to a prolongation of the rear axle of the bicycle. A side view of the apparatus, as partially dismantled and mounted in the chair calorimeter, is shown in figure 1. In order to save space in the chamber, the front handle bars and fork have been removed. Another view of the apparatus, as seen from above, is shown in figure 2. For further details regarding the apparatus, reference must be made to the detailed and diagrammatic figures given by Krogh in his description.

To simplify calculations the exact distance between the centre of the axle to the point of suspension of the pan upon which the weights are placed has been made equal to 0.3182 meters. By means of a screw counterpoise the weight of the arm and pan can be accurately compensated and the whole system brought into perfect equilibrium. If, then, a weight is placed upon the pan and a current passed through the fields, when the disk is rotated the pan and weight will be elevated and suspended free in the air. With a considerable strength of field current there will be a drag upon the magnets which will ultimately raise a weight as large as 6 kilograms and hold it in equilibrium. Under these conditions the work per revolution will be represented by the weight on the pan multiplied by the circumference of a circle of which the hub of the wheel is the centre and the point at which the pan is

suspended is on the circumference. The ergometer is so constructed that the circumference of this circle is exactly 2 meters. Thus, for every revolution of the wheel with a weight of 1 kilogram on the pan, there will be 2 kilogrammeters of work performed.

Krogh first depended upon hand regulation for adjusting the cur-

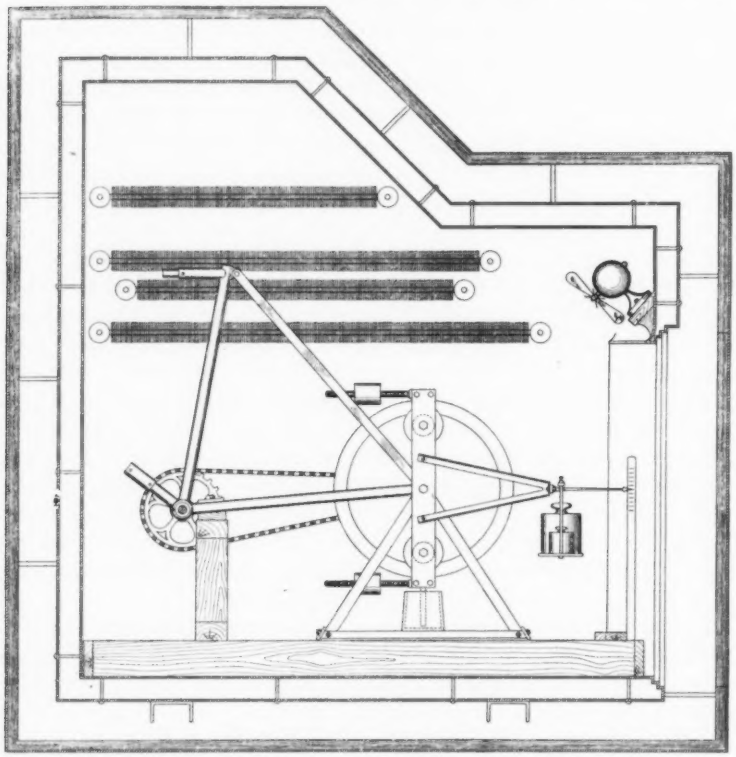

Fig. 1. Krogh bicycle ergometer as mounted for calibration in the chair calorimeter. (Side view.)

rents through the magnets to hold the balance system in equilibrium and while he subsequently applied an automatic arrangement, hand regulation was used in all of our tests. To prevent gross movements of the system due to the irregularity of pedaling by a man, Krogh has also added a damping device which consists of a heavy sheet of

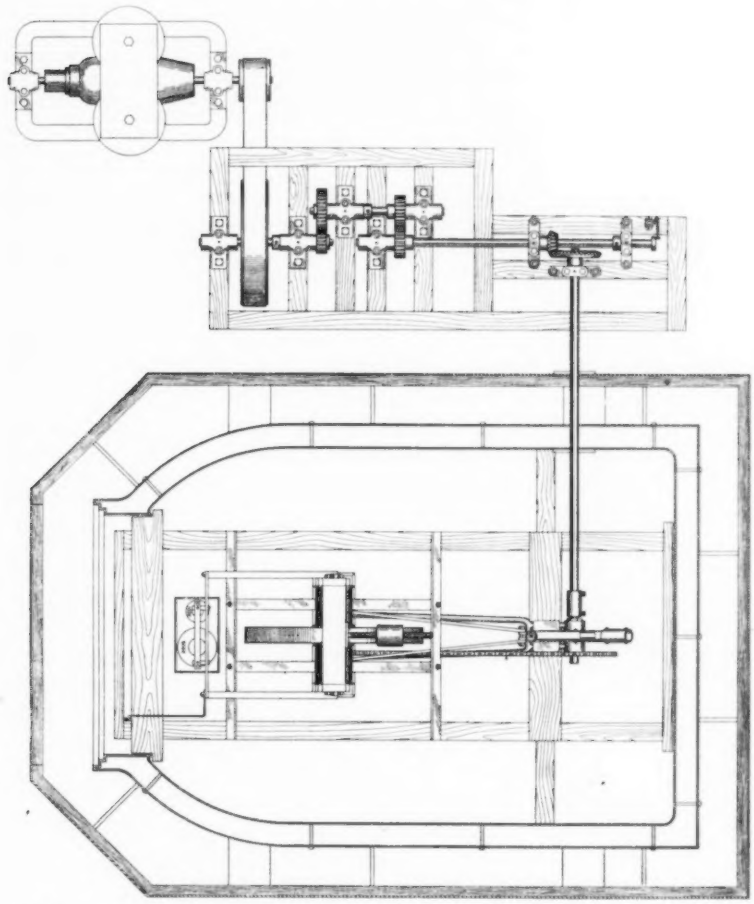

Fig. 2. Krogh bicycle ergometer as mounted for calibration in the chair calorimeter. (View from above.)

lead attached to the magnet frame. This lead paddle dips in a trough containing a thick syrup solution. While this damping device is of advantage in the practical use of the apparatus, in calibrations of the ergometer in which the apparatus is driven by an electric motor, irregularities of movement do not exist and hence it was unnecessary to employ the damping device in the calibrations.

The Krogh apparatus permits very considerable variations in the amount of work performed. Thus Krogh has shown that as large an amount of work as 2900 kilogrammeters per minute may readily be done upon the apparatus. It seemed desirable in our observations, therefore, to calibrate over a considerable range and we were at once confronted by the fact that while the chair calorimeter, which was used for these calibrations, is normally not used for experiments in which the total heat production—that of a sitting man—is much, if any, over 125 calories per hour, here we had to consider the possible production of 6 large calories per minute, exclusive of the heat developed in the fields of the magnets by the magnetizing current and the heat due to a small electric fan, which is used in securing temperature equilibrium inside the chamber. A more extended system of heat absorbers was therefore required for these tests and accordingly the ordinary heat absorbing system, which is shown in the original description of the chair calorimeter,[15] was supplemented by several lengths of heat absorbing coil, making a total length of 8.7 meters. The disposition of these extra coils is clearly shown in figure 1.

Under these changed conditions, it was necessary to test the respiration chamber calorimetrically by developing 6 calories per minute electrically inside the chamber. We therefore checked all of the calibrations of the ergometer by making electrical check tests in which approximately the same amount of heat was developed as was actually developed in the ergometer calibration. The electrical check tests were usually three to five hours in length and the heat measured varied from 150 to 350 calories per hour. The results showed that as a calorimeter the apparatus had a very high degree of accuracy.

In mounting the apparatus it was of course necessary to have the driving mechanism outside of the chamber and for this purpose a shaft was carried through the copper wall[16] of the calorimeter and attached directly to the pedal bearing of the ergometer. By means of a system of reduction gears, which varied somewhat with the speeds employed, this shaft was connected with a 2 kilowatts electric motor outside of the calorimeter. The connection between the motor, gearing, and the ergometer is shown in figure 2. A revolution counter attached to

[15] Benedict and Carpenter: Carnegie Institution of Washington Publication No. 123, 1909.

[16] To prevent interchange of heat along the shaft the temperature of the calorimeter laboratory was always kept the same as that of the interior of the calorimeter.

the reduction gear shaft recorded the number of revolutions of the pedal per minute. The weights on the swinging pan of the ergometer could be varied as desired. The arm of the pan was projected somewhat by the pointer which was held in equilibrium by variable resistance outside the chamber in parallel with the magnets.

To equalize temperature distribution inside the chamber, an electric fan has been found advantageous in practically all of our work with the calorimeters, and was retained in the calibration tests. The heat brought away by the cooling water current of the calorimeter included the heat developed as a result of the mechanical work, plus the electric energy required to magnetize the fields and the heat developed by the fan. In our final computations these two latter factors are deducted. Throughout the entire series of calibration tests, frequent records were

TABLE 1

Results of calibration test of Krogh bicycle ergometer, December 10, 1914

TIME	WEIGHT OF WATER	CORRECTED TEMPERATURE DIFFERENCE	TOTAL HEAT MEASURED	CORRECTION FOR CHANGE IN TEMPERATURE OF CALORIMETER	HEAT DUE TO CURRENTS IN MAGNETS AND FAN	CORRECTED HEAT MEASURED	TOTAL NUMBER OF REVOLUTIONS OF DISK	HEAT PER REVOLUTION
p. m.	*kilos.*	*°C.*	*cals.*	*cals.*	*cals.*	*cals.*		*cals.*
12.26–1.26	80.67	4.432	357.5	−1.0	85.8	270.7	9627	0.02812
1.26–2.26	80.65	4.310	347.6	−0.4	90.7	256.5	9024	0.02842
2.26–3.26	80.62	4.242	342.0	+0.8	92.7	250.1	8874	0.02818

made of the voltage and current on the fan and likewise that required to magnetize the fields of the ergometer. With a rate of revolution so constant as that obtained with an electric motor, the variations in the magnetizing current would be very slight and readings every four minutes could be relied upon to give an average value throughout the experiment.

The results of a specimen experiment are given in Table 1. In this experiment the load on the pan was 6 kilograms. There were 47.0 revolutions per minute of the pedals, which corresponded to 152.9 revolutions per minute of the disk or rear wheel, as the ratio of the pedals to the rear wheel is 1 to 3.25. This ratio was obtained by the number of teeth on the sprockets, the large sprocket having 26 teeth and the smaller sprocket 8 teeth. In the first column of the table is given the time for each period; in the second the weight of water passing through the cooling system; in the third the temperature difference corrected

for pressure on the thermometer bulbs; and in the fourth the total calories measured. Slight capacity corrections are shown in column five, the heat required for magnetizing the fields and for the fan is given in column six, and in column seven is given the corrected measurement, i.e., the total calories measured less the capacity correction and the heat due to the magnetizing of the fields and to the fan. The total number of revolutions of the disk or rear wheel is given in the next to the last column and finally the calories per revolution are computed.

It will be seen that in the three 1-hour periods the heat measured per revolution was 0.02812, 0.02842, and 0.02818 large calorie respec-

TABLE 2

Results of calibration tests of the Krogh bicycle ergometer, made with the chair calorimeter

DATE	DURATION OF TEST	LOAD	REVOLUTIONS PER MIN. OF PEDALS	REVOLUTIONS PER MIN. OF DISK	HEAT PER REVOLUTION OF DISK		
					Found	Theory	Ratio of found to theory
1914	*hrs.*	*kilos.*			*cals.*	*cals.*	*per cent*
Dec. 10.....	3	6	47.0	152.9	0.02824	0.02813	100.4
Dec. 14.....	4	6	43.4	141.2	0.02828	0.02813	100.5
Dec. 16.....	3	6	58.2	189.2	0.02814	0.02813	100.0
Dec. 17.....	3	3	124.6	405.1	0.01414	0.01406	100.6
Dec. 31.....	3	3	84.3	274.1	0.01406	0.01406	100.0
1915							
Jan. 1.....	3	2	144.5	469.7	0.00946	0.00938	100.9
Jan. 4.....	3	4	82.7	268.8	0.01880	0.01875	100.3
Jan. 8.....	4	5	70.1	227.9	0.02351	0.02344	100.3
Jan. 9.....	4	1	144.3	469.1	0.00479	0.00469	102.1
Jan. 11.....	4	1	105.3	342.2	0.00471	0.00469	100.4

tively, with an average of 0.02824 large calorie. Since each revolution of the disk was equivalent to the load (6 kilograms) multiplied by the circumference of the circle (2 meters), we have here 12 kilogrammeters as the amount of work done. Using 426.6 kilogrammeters[17] as the equivalent of 1 large calorie, we find that 12 kilogrammeters correspond to 0.02813 large calorie. Thus in this particular experiment we find that the ergometer produced 100.4 per cent of the theoretical energy computed from the weight on the pan and the revolutions of the disk.

The results of all of the ergometer calibrations have been summarized in Table 2. The tests included calibrations with weights on the pan

[17] Armsby: Principles of animal nutrition, New York, 1906, p. 233.

ranging from 1 to 6 kilograms and with revolutions of the pedals per minute varying from 43.4 to 144.5 and of the disk or rear wheel from 141.2 to 469.7. In other words, the tests include great varieties of speed and weight, extending quite outside the range of ordinary physiological experimentation. It will be seen that the percentage of theory found with this ergometer is striking, the average of the 10 tests being 100.55 per cent with variations from this value exceeding 1 per cent in only one instance. Since the rate of speed and the load were so greatly varied, it is reasonable to conclude that the friction plays a wholly insignificant rôle with this instrument and may accordingly be entirely neglected in any computations of the work done. With the Krogh ergometer, it is therefore justifiable to use without corrections the formula

$$W = 2pR$$

in which W is the work in kilogrammeters, p is the weight in kilograms and R the number of revolutions of the rear wheel.

SUMMARY.

A Krogh electric brake bicycle ergometer was placed inside of a bed calorimeter and rotated from the outside by means of an electric motor. The heat developed was measured by the calorimeter and has been compared with the computation of the work done in sustaining various loads on a suspended balance pan. These experiments showed that friction and other extraneous factors may be entirely neglected in using the Krogh bicycle ergometer and that the results obtained by calibration were within 0.5 per cent of theory. The experiments included tests at different rates of speed and with different weights on the balance pan.

THE EFFECT OF ADRENALIN ON THE HEART-RATE

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In a previous article[1] we have attempted to determine some of the mechanisms by which the immediate increase in pulse-rate at the beginning of a period of exercise is brought about. Our conclusions were that the increase in rate is produced principally by a decrease in vagal tone. Although acceleration may take place through the accelerators the evidence seemed to indicate that they act chiefly in maintaining the resting pulse-rate and that their accelerating action is a factor of safety superimposed on the more labile vagus mechanism. Incidental to this work we were able to make some observations on the action of the adrenals.

Animals with the accelerators removed and the vagi cut did not show a noticeable increase in heart-rate unless there were symptoms of asphyxia. Soon after the vagotomy when the signs of respiratory distress were most marked, exercise produced a great increase in pulse-rate. In the succeeding days as the signs of asphyxia decreased the exercise acceleration grew very much less. That the marked increase of rate had been due to the asphyxial secretion of the adrenals we proved by ligating these organs. Since the adrenalin seemed to be a factor only when exercise was pushed to an extreme we concluded that in the normal animal with the vagi intact the secretion of adrenalin could hardly be considered as one of the mechanisms which immediately increase the heart-rate on exercise. We still believe this holds for moderate exercise when uncomplicated by emotional excitement.

It is to be noted that our argument does not rest on the fact that adrenalin as usually given experimentally produces cardiac inhibition if the vagi are intact, but that the conclusions are based on our direct experiments. In our discussion we did overlook the fact however that as exercise increased in amount and the vagus tone grew less and less

[1] Gasser and Meek: This Journal, 1914, xxiv, p. 48.

there must of course come a time when any secretion of adrenalin might have an accelerating effect on the heart-rate.

Recently Hoskins and Lovellette[2] have objected to any conclusions that adrenalin does not always cause acceleration in exercise on both theoretical and experimental grounds. They point out in the first place that the doses of adrenalin experimentally shown to give inhibitory effects have been far in excess of the physiological secretions determined by their previous work. The rate of injection too has been much more rapid than the normal adrenal discharge. There is no gainsaying these important and just criticisms which, however, we feel do not apply to the experimental part of our work.

In the second place Hoskins and Lovellette present a table of 28 experiments on dogs in 18 of which there is increased heart-rate following the injection of adrenalin in physiological amounts. An examination of their data shows that the initial pulse-rate was in all cases very high. The lowest rate recorded is 144 per minute and the highest 258. The average is 188 per minute. This indicates a low vagal tone which was to be expected from the ether anaesthesia. It is by no means surprising that under these conditions 18 of the dogs showed an increase in heart-rate with small doses of adrenalin. That the heart itself is exquisitely sensitive to adrenalin we have had occasion to observe in work on the isolated heart. As soon then as the vagus mechanism becomes sufficiently depressed and the secretion of adrenalin becomes sufficiently large stimulation of the heart would of course result. The animals of Hoskins and Lovellette represent therefore to our mind a picture of extreme exercise, the decrease in vagal tone in their case being due to the ether anaesthesia. Limited to such conditions their conclusions are eminently correct. Adrenalin in a time of extreme muscular exertion when the decrease in vagal tone has done all the accelerating it can, is then able to show its direct stimulating effect on the heart muscle.

Although our previous work seemed to show that in dogs the adrenals were not concerned in any large degree in the increased pulse-rate which resulted from two minutes running, it has seemed worth while to study directly the effect of adrenalin when injected in small amounts into the unanaesthetized animal.

To accomplish this the dogs were laid on the floor and held until they had become perfectly quiet. The injection was made into an ear vein by a hypodermic needle which was connected with a burette,

[2] Hoskins and Lovellette: Journal of the American Medical Association, 1914, lxiii, p. 316.

the fluid being under air pressure in the burette. By means of this pressure and the proper opening of the burette cock, the injection could be made absolutely regular and at any desired speed. Usually the needle could be inserted without the dog even moving. In case the animal flinched at the prick of the needle, it was again quieted before the experiment proceeded. The right front and left hind leg of the dog were connected to the string galvanometer and electrocardiographic records of the heart-beat were taken at one-half intervals immediately before, during and from two to four minutes after the injection ceased. Each record was at least one respiratory cycle long, usually several being included, in order to avoid respiratory variations obscuring the count.

Adrenalin hydrochlorid and crystalline adrenalin were used. The amount injected varied from 2–3 cc. and the strength from 1: 50,000 to 1: 500,000. The duration of the injections varied from 1 minute 20 seconds to 3 minutes 55 seconds. These quantities were chosen so that the injection might simulate in some degree at least the physiological secretion.

The results of our experiments are presented in Table 1. It will be seen that in 25 injections on nine different dogs, in all but two the heart was slower at the end of the injection than at the beginning. Even these two cases are really not exceptions for in experiment 5^3 the rate was as low as 55 per minute during the second minute of the injection. By the end of the injection it had however risen to its former level. In experiment 9^3 also the rate at the end of the first minute had dropped to 102 but by the end of the injection it had risen to 132 per minute. In all cases then a slow injection of adrenalin in doses approximating its physiological secretion has given us in the intact resting animal a slowing of the pulse.

According to the generally accepted belief that this slowing takes place as a reflex through the vagus, we should expect less effect in those cases with a depressed vagus mechanism, i.e., those hearts with a high rate due to loss of vagal tone. The data bear this out in a few instances rather definitely. Variations in dose and time of injection make only a few comparisons possible, but in experiment 3 it may be noted that a rate of 150 was reduced only to 141 while under almost identical conditions a rate of 129 fell to 108.

The pulse rates for the successive half minutes show that the effect of adrenalin in these doses comes on in from one-half to one minute after the injection starts. With the higher dilutions particularly the

pulse-rate may begin to increase again before the injection is ended. For this reason the table does not always give the lowest rate recorded. With the stronger concentrations the heart did not begin to resume its normal until the injection was finished.

TABLE 1

Showing the influence of adrenalin in small doses on the pulse-rate of nine unanaesthetized dogs. In experiments 7 and 8 crystalline adrenalin was used; in all others adrenalin hydrochlorid. The exponents represent successive injections in the same experiment

EXPERIMENT NO.	PULSE RATE AT BEGINNING	CC. INJECTED	STRENGTH	LENGTH OF INJECTION	PULSE RATE AT END OF INJECTION
1	88	3.5	1: 50,000	3′	64
2	140	3.0	1: 50,000	2′ 30″	65
3^1	93	3.0	1: 50,000	2′ 40″	60
3^2	69	3.0	1: 50,000	2′ 20″	45
3^3	100	3.0	1: 100,000	2′ 10″	90
3^4	129	2.5	1: 100,000	3′	108
3^5	150	3.0	1: 100,000	3′ 05″	141
4^1	124	3.0	1: 100,000	1′ 30″	90
4^2	138	3.0	1: 50,000	1′ 30″	70
4^3	122	3.0	1: 50,000	3′ 55″	90
5^1	72	3.0	1: 50,000	1′ 55″	68
5^2	87	3.0	1: 500,000	1′ 20″	60
5^3	67	2.0	1: 100,000	3′ 45″	67
6^1	99	3.0	1: 100,000	2′ 35″	66
6^2	90	3.0	1: 500,000	1′ 40″	75
6^3	86	2.0	1: 500,000	3′	78
7^1	96	2.5	1: 50,000	2′	66
7^2	90	2.0	1: 200,000	1′ 50″	48
8^1	108	2.0	1: 50,000	1′ 05″	75
8^2	99	2.0	1: 50,000	1′ 55″	72
8^3	117	2.0	1: 200,000	2′ 15″	96
8^4	120	2.0	1: 200,000	1′ 45″	84
9^1	117	2.0	1: 50,000	1′ 35″	66
9^2	123	2.0	1: 50,000	2′ 05″	96
9^3	123	2.0	1: 200,000	2′ 10″	132

The pulse-rate was followed in all cases for from one to four minutes after the injection. In nearly all experiments the heart had reached its former rate or exceeded it by the end of the third or fourth half-minute. In 12 of the 25 separate injections the rate after the injection had been finished rose somewhat above its previous level.

SUMMARY

Intravenous injection of physiological amounts of adrenalin into intact unanaesthetized dogs with good vagal tone invariably causes a decrease in the heart-rate.

The action of the adrenalin is doubtless twofold; it accelerates the heart by direct stimulation and inhibits it reflexly through the vagus. In our experiments the net result of this balanced mechanism was always a decrease in pulse-rate.

For this reason a secretion of adrenalin could hardly play a part in the immediate cardiac acceleration which follows moderate exercise.

In exercise which has been pushed to an extreme degree, however, the accelerating action of adrenalin might well become predominant, for in this condition we have a great decrease in vagal tone. In regard to the heart-rate then adrenalin seems to act just as it does in so many other instances; that is its stimulating effect becomes apparent at a time of great physiological need.

THE INFLUENCE OF THE OIL OF CHENOPODIUM ON THE CIRCULATION AND RESPIRATION

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The frequent occurrence of circulatory and respiratory disturbances observed in the course of studies on the toxicity of the oil of chenopodium (1), (2) suggested the present investigation. The experiments were carried out on different animals, several anesthetics being used for the operative procedures. Morphine-ether anesthesia or chloretone in alcohol was employed in experiments on dogs, ether alone was given to cats, while rabbits were anesthetized with ether or urethane, the latter being given by mouth through a stomach tube.

The oil of chenopodium was introduced in the form of 1 or 2 per cent emulsion, which was made up by adding the oil to 0.9 per cent salt solution, usually but not always containing 5 per cent of acacia, 1 per cent cocoanut oil, and a few drops of sodium carbonate solution. The mixture was then vigorously agitated in a shaking machine until a very fine emulsion resulted. This was injected into the femoral vein from a burette. An emulsion containing all the ingredients in the same proportion, but without chenopodium, was used as a control, and was injected into the femoral vein on the opposite side. It may be stated in advance that blood pressure, after the administration of the control solution, was only slightly increased or not affected at all. No change in respiration was observed at any time. The injections were made from 50 cc. graduated burettes which were held in a Liebig condenser containing water that was maintained at body temperature or a little below by allowing it to circulate through a glass jar, the contents of which were kept warm by means of an electric bulb immersed in the liquid. Blood pressure was recorded by a mercury manometer connected with the carotid artery in the usual fashion, a saturated sodium sulphate solution being used as an anti-coagulating fluid. Respiration was recorded by two receiving tambours, one applied to the thorax

and the other to the abdomen, each of these being connected with a recording tambour by means of rubber tubing. In some experiments the respiration was recorded by a tambour connected with the trachea.

The volume of the kidney was recorded by means of the Roy oncometer in the earlier experiments but air transmission alone was substituted later, the kidney being placed into a covered aluminum box provided with an opening for the renal pedicle. By means of lanolin, the oncometer was made air-tight. One end of a brass tube was fitted into an opening in the top of the oncometer, the other end being connected by means of rubber tubing, with a recording tambour. Variations in volume of the kidney could thus be readily observed.

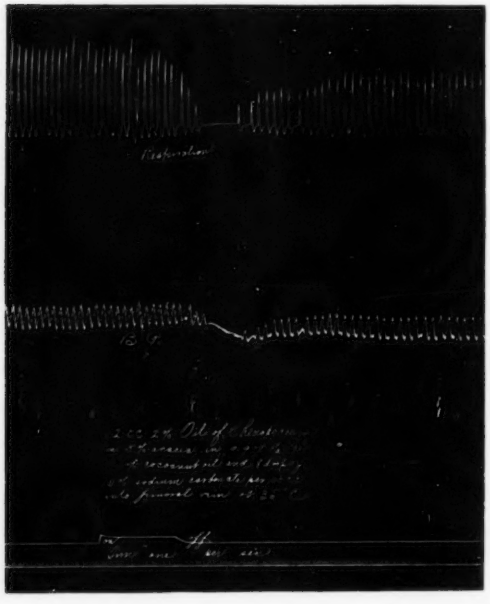


Fig. 1. Dog 218. First injection of 0.02 cc. chenopodium per kilo. Fall of blood pressure, apnoea, and decreased amplitude and rate of respiration.

EXPERIMENTS ON DOGS

Effect on the circulation

A fall of blood pressure, varying in extent and duration was usually observed after the intravenous injection of the oil of chenopodium. In experiments in which morphine-ether was employed, the initial dose of 0.02 cc. per kilo caused a decrease in blood pressure of 10 to 15 mm. Hg or 7.5 to 10 per cent (fig. 1). When a second injection was made, the effects of the same amounts were more pronounced. The fall of blood pressure increased from 7.5 to 12 per cent in one experiment, in another from 10 to 24 per cent, in a third from 9 to 14 per cent, there being little or no difference in the speed of in-

jection. In one experiment, however, the effect was more marked, and was also reversed, the initial injection of the same dose having produced a fall of blood pressure amounting to 35 per cent, while a second injection produced a fall of blood pressure of 16 per cent.

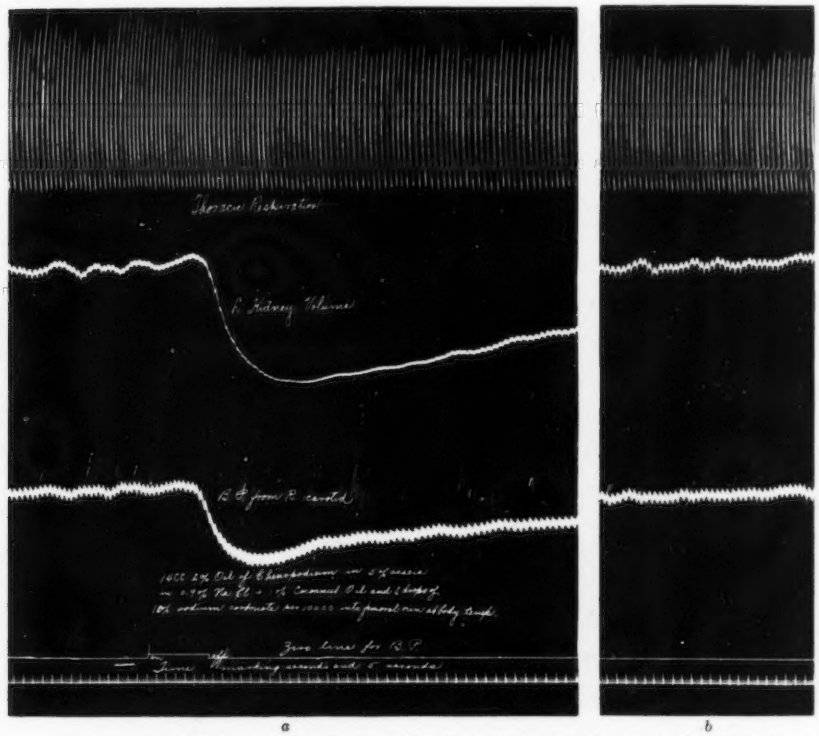


Fig. 2. (*a*) Dog 221. Chloretone—alcohol anesthesia. Marked fall of blood pressure and diminished volume of kidney after the injection of 0.02 cc. chenopodium per kilo. Respiration only slightly depressed. (*b*) Also shows recovery 15 minutes later.

When anesthesia was produced by means of chloretone and alcohol, the initial injection of 0.02 cc. oil of chenopodium per kilo decreased blood pressure 40 to 50 per cent (fig. 2). A second dose, given after an interval of 30 minutes, was followed by the same effect in one experiment, but in two others blood pressure fell considerably less, the

decrease being 20 instead of 50 per cent in one experiment, and about 30 per cent in another in which the initial injection caused a fall of blood pressure of 65 per cent.

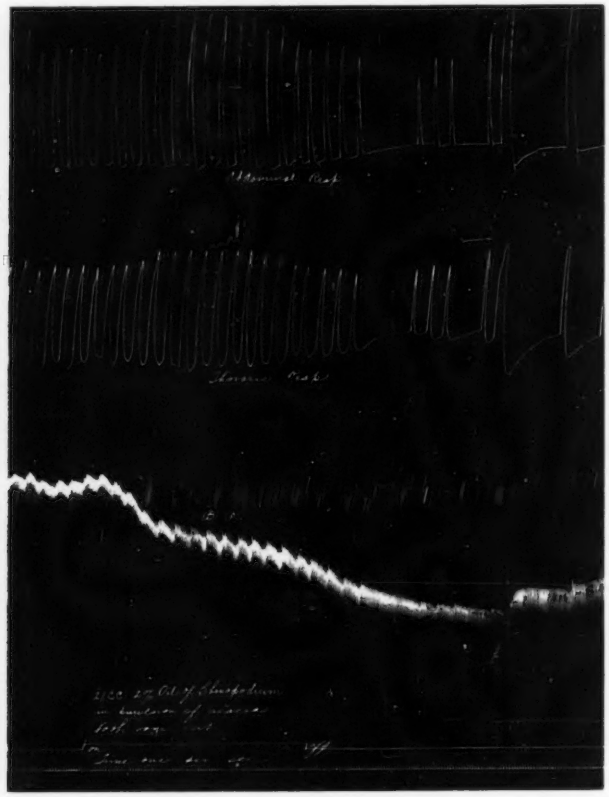


Fig. 3. Dog 210. 0.06 cc. chenopodium per kilo. Showing marked fall of blood pressure and apnoea.

A number of experiments with larger doses have also been carried out. The initial injection of 0.05 and 0.06 cc. oil of chenopodium per kilo produced in dogs, under morphine-ether anesthesia, a fall of blood pressure from 160 mm. to 80 mm., or 50 per cent in one experiment (fig. 3). In another it fell from 155 to 120 mm., or 21 per cent, although

the rate of injection in both was the same, being 1 cc. in about four seconds. In a third subject, likewise under morphine-ether anesthesia, in which the speed of injection was 1 cc. in 16 seconds, 0.05 cc. oil of chenopodium per kilo produced a fall of blood pressure from 115 to 75 mm., or 34 per cent. It is evident, therefore, that the rate of injection does not modify the action of oil of chenopodium on blood pressure. Similar results were obtained with smaller doses in several experiments. The rate of injection is an important factor, however, in determining the character of the fall of blood pressure, which was abrupt when carried out rapidly, but gradual when the speed was reduced.

The effect of repeated injections varied in our experiments, a second dose of the same size, as already noted, producing in some cases an increased fall of blood pressure. In others, on the contrary, this was much less than that caused by the previous initial injection. Subsequent injections decreased the reaction to chenopodium until the response of the circulation completely disappeared (fig. 4) even when larger amounts were introduced. Although the quantity required to produce this effect varied in different individuals, a progressive decrease in the intensity of the reaction was observed until blood pressure was no longer affected by chenopodium. This condition was usually attained when the total amount received exceeded 0.2 cc. per kilo, although in two experiments the depression of the circulation was only slightly affected after doses of 0.105 and 0.12 cc. per kilo had been introduced. The action of repeated injections is illustrated in the following experiments:

In one experiment a dose of 0.085 cc. per kilo produced a maximum fall of blood pressure of 55 per cent. The decrease in the next injection of the same amount was 35 per cent, but after the following injection the fall of blood pressure was only 20 per cent.

In another experiment (fig. 3) the initial injection of 21 cc., or 0.06 cc. per kilo, produced a fall of blood pressure of 50 per cent, and only 7 per cent at the seventh injection when the same dose was given, the total amount previously injected being approximately 0.3 cc. In the same experiment 0.04 cc. per kilo, given in a third injection was followed by a fall of blood pressure of 48 per cent. Such a dose given in the eighth injection had no effect on blood pressure, the rate of injection being practically the same.

In a third experiment 0.02 cc. per kilo, introduced in 15 seconds at the fifth injection, caused a fall of blood pressure, amounting to 20 per

cent. Double this dose per kilo at the tenth and eleventh injections, after a total of 0.236 cc. had been given, failed to produce any change in blood pressure.

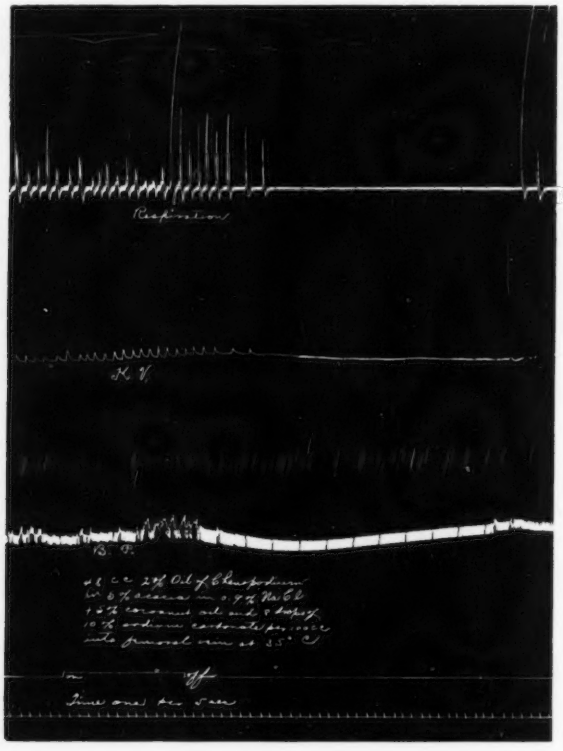


Fig. 4. Dog 219. Prolonged apnoea; 3¾ minutes after injection of chenopodium, then dyspnoea. Blood pressure not affected by the injection of 0.08 cc. chenopodium per kilo. Total amount previously injected 0.24 cc. per kilo.

In a fourth experiment 0.04 cc. per kilo, injected in 35 seconds, lowered blood pressure 20 per cent at the sixth injection. A dose of 0.085 cc. per kilo, given at the ninth injection, produced a rise of blood pressure of 11 per cent (which might be expected if the same volume of the control solution were injected). Such a dose injected 34 minutes previously lowered blood pressure 25 per cent.

Similar results were obtained in several other cases. The condition of the blood pressure at the time the failure to respond to oil of chenopodium occurs may appear to be an important factor in the determination of this result, for blood pressure at the time of the injection was considerably lower than at the beginning of the experiment. Analysis shows, however, that this is not the case. In two experiments in which blood pressure fell from 130 to 85 mm. Hg. approximately the same amount of chenopodium produced a fall of blood pressure, in one case 35 per cent, in the other 23.5 per cent. In three subjects in which blood pressure fell from 155–160 mm. Hg. at the beginning of the experiment to about 100 mm. Hg, the reaction to chenopodium was fairly good in two, a fall of blood pressure of 35 per cent being observed in one case after injecting one gram, or 0.085 cc. per kilo. In another 0.06 cc. per kilo produced a fall of blood pressure of 30 per cent. In a third 0.04 lowered blood pressure 10 per cent.

It is evident, therefore, that the reaction to chenopodium may persist though blood pressure had fallen one-third. The experiments carried out under alcohol chloretone anesthesia afford additional evidence that the reaction of the circulation to oil of chenopodium is not determined by the height of the blood pressure, for it will be recalled that small quantities caused a very marked effect when the maximum blood pressure was only 100 mm. Hg, while in many instances in which the height of the blood pressure was 40 to 50 mm. Hg, or even less, the administration of oil of chenopodium produced depression of the circulation to a very considerable degree. Decreased reaction or complete failure of the circulation to react to drugs after repeated injections have been reported by several investigators. Sollmann and Pilcher (3) observed in dogs that large doses of caffeine lowered blood pressure to 50 or 60 mm. Hg, but additional injections failed to cause a further decrease. This is attributed by them to the low blood pressure preceding the injection, since a dose of caffeine which was without effect when blood pressure was under 45 mm. Hg produced a considerable change if injected during periods of high blood pressure. Blackford and Sattford (4) found that the initial dose of an extract of goitre lowers blood pressure in dogs but subsequent injections produced little or no effect. Roth (5) reported similar observations recently with Pituitrin in different animals.

Changes in the volume of the kidney indicate that the fall of blood pressure is of cardiac origin since the oncometric records have almost always varied directly with the changes in blood pressure, being almost

parallel after some injections (fig. 2). In some experiments in which blood pressure no longer reacted to oil of chenopodium, its introduction into the blood stream, especially when large amounts were injected, was followed by an appreciable increase in volume of the kidney, although smaller quantities failed to produce similar changes. That cardiac depression was produced by chenopodium was also indicated by a significant reduction in the rate of heart action, which may be seen on examination of figures 6 and 7. A marked decrease in cardiac vagus irritability was obtained, even after moderate doses were administered. When the vagi were divided after the large amounts of oil of chenopodium were injected, blood pressure rose a few millimeters or remained unchanged.

Fig. 5. Dog 209. 0.021 cc. chenopodium per kilo. Apnoea, with decreased respiratory amplitude and fall of blood pressure.

Effect on respiration

The intravenous injection of the oil of chenopodium was likewise followed by depression of respiration. This varied with the size of the dose and sometimes also with the speed with which it was introduced into the blood stream. Small doses, 0.02 to 0.028 cc. oil per kilo of body weight, produced with few exceptions, a decrease in the amplitude, the rate of respiration being affected much less frequently when such amounts were introduced directly into the circulation. In some instances arrest of respiration for a brief period (Dog 209, fig. 5), with prompt recovery was observed. The activity of larger doses was much more marked. The injection of 0.04 cc. oil of chenopodium per

kilo produced slowing of respiration more frequently than with small doses, the amplitude of thoracic respiration being decreased considerably at the same time. The effect on abdominal respiration was less pronounced (fig. 6, Dog 210). Very striking results were noticed in

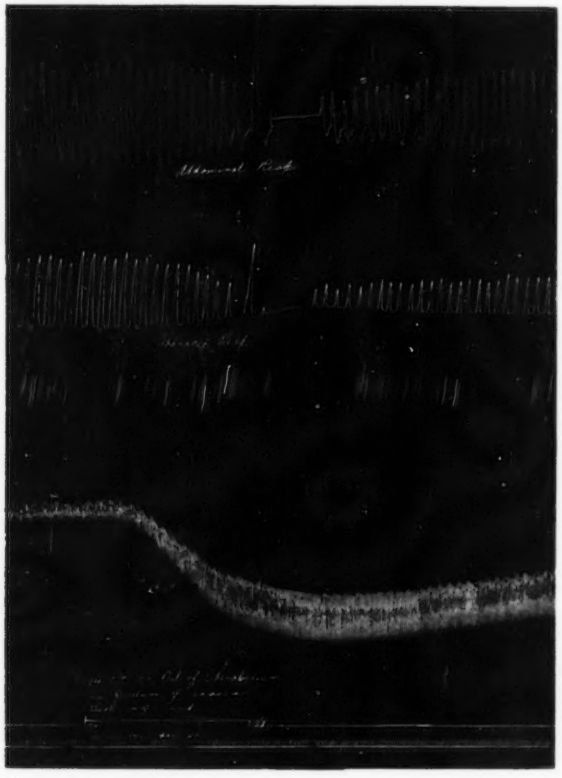


Fig. 6. Dog 210. Apnoea. Respiratory amplitude decreased. Marked fall of blood pressure after the injection of 0.04 cc. chenopodium per kilo.

some experiments (fig. 7), when the doses were still more increased. After the injection of 0.06 cc. oil of chenopodium the rate was very frequently diminished; the amplitude of thoracic respiration also showed considerable reduction, abdominal respiration, however, being much less

affected in this case. The initial injection of such a dose, produced apnoea which lasted nearly 20 seconds. Respiration improved at the end of this time but the rate was only 50 per cent of that preceding the

Fig. 7. Dog 210. Showing prolonged apnoea and diminished frequency of respiration after the intravenous injection of 0.085 cc. chenopodium per kilo. Also marked fall of blood pressure and slowing of heart action.

injection. Recovery took place in two minutes. A second injection of 0.085 cc. per kilo (Dog 210, fig. 7), given 16 minutes later caused apnoea which lasted about 50 seconds. In another experiment the initial injection of the same dose was followed by a decrease of frequency of

about 50 per cent. The amplitude of thoracic respiration decreased about 25 to 30 per cent. Abdominal respiration, on the other hand, became more prominent in this case.

The action of repeated injections indicated a tendency to cumulative effect. Even after complete recovery from previous treatment was obtained, another dose of the same size was followed by a more pronounced depression of respiration which was obtained with small, as well as with large doses.

Observations were also made on the effect of the speed of injection. When 0.02 cc. per kilo were introduced at the rate of 15 to 30 cc. per minute the action was practically the same, but the introduction of 0.05 cc. to 0.06 cc. per kilo, given at the rate of 7.5 cc. to 18.0 cc. per minute, showed differences that were very striking. The slower injections of small and of large amounts produced a slight decrease of amplitude of thoracic respiration which was preceded by slight stimulation, but rapid injections were followed in the case of small doses by a marked reduction in rate and decrease in amplitude of thoracic respiration lasting more than $1\frac{1}{2}$ minutes, while large doses were followed by apnoea lasting about a half minute and disturbed rhythm with diminished frequency of respiration from which it recovered in about $2\frac{1}{2}$ minutes.

It will be observed, therefore, that the behavior of the respiratory mechanism towards chenopodium presents important differences from that of the circulation. While the latter frequently showed a tendency towards lessened response after one or two injections of moderate amounts have been made, as already pointed out, the reaction to chenopodium finally disappearing altogether even after large doses have been introduced, respiration, on the contrary, became increasingly slower until it was arrested altogether after the administration of amounts that were much less effective in the earlier stages of the experiment. Blood pressure and cardiac action, which have nearly always been fairly good at the time oil of chenopodium ceased to be effective for the circulation, continued with little or no change for a considerable period of time, while respiration manifested signs of increased disturbance. In some experiments the frequency of the heart beat was still well within the normal rate at this time, the blood pressure being 50 mm. Hg and in some experiments reaching a height of 80 to 90 mm. Hg for about $2\frac{1}{4}$ minutes after respiration had ceased (Dog 219, fig. 4).

Prolonged periods of apnoea were also observed in the final stages

of most of our experiments, usually a short time after the last dose of oil of chenopodium. In one experiment apnoea set in 2½ minutes after the final dose and lasted 3½ minutes. The heart stopped at the end

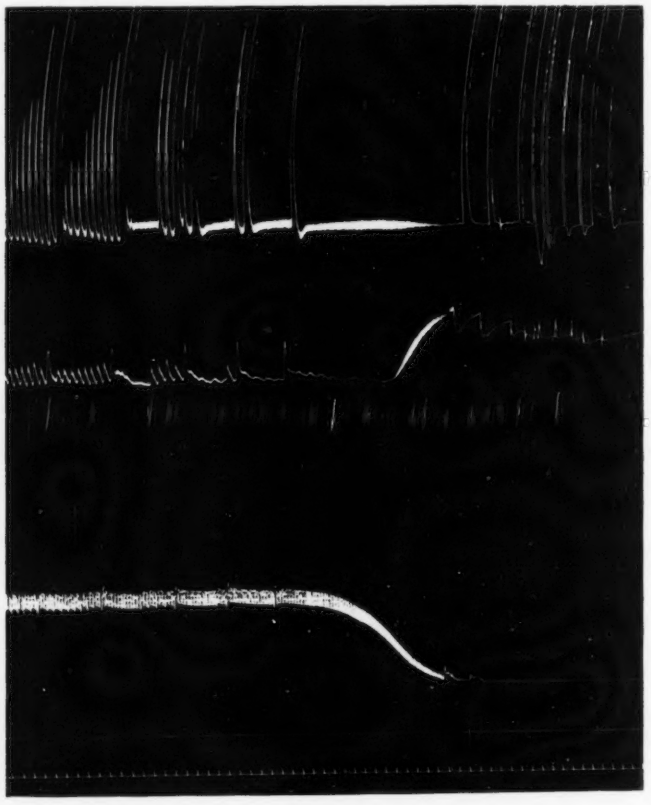


Fig. 8. Dog 220. Apnoea (upper curve). Cardiac paralysis (lower curve) and dyspnoea. Middle curve shows kidney volume. Time, 5 seconds (lowest line).

of this period, apnoea being succeeded by well marked dyspnoea which lasted 2 minutes. In another experiment (fig. 8) 6 minutes after the final dose, which was 0.08 cc. per kilo in this case, several periods of apnoea varying between 20 to 80 seconds were observed, blood pressure during this time was 55 mm. Hg. As blood pressure fell apnoea was

at once followed by dyspnoea and death. This sequence of events, prolonged apnoea, cardiac paralysis, and dyspnoea was observed in most experiments on dogs.

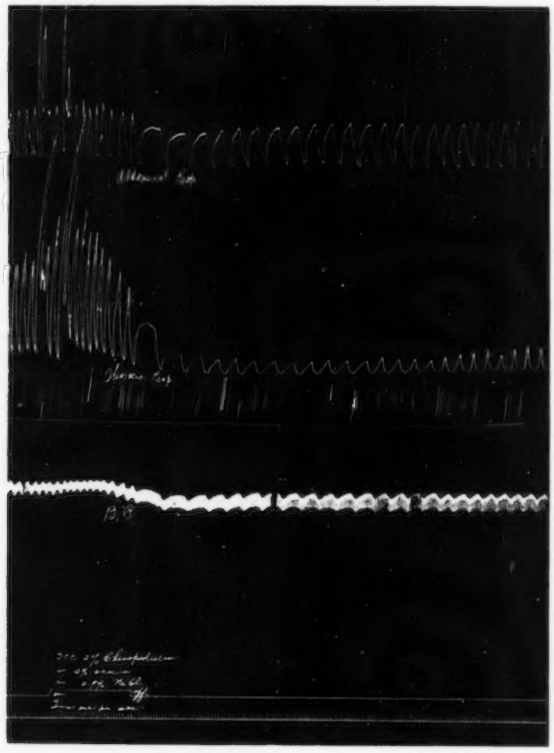


Fig. 9. Cat 287. Intravenous injection of 0.04 cc. chenopodium per kilo. Moderate fall of blood pressure with marked depression of respiration.

EXPERIMENTS ON CATS

The action of the oil of chenopodium when given intravenously was somewhat different in cats. Its effect on respiration was more marked than in dogs. The initial injection of 0.02 to 0.04 cc. per kilo (fig. 9), produced a fall of blood pressure of 6 to 8 per cent, while respiration was depressed to a marked degree, the amplitude, as well as the

rate having been decreased very considerably. A second injection produced a greater effect. Blood pressure fell nearly 10 per cent after smaller doses and 25 per cent after larger doses. Thoracic respiration ceased immediately after injection; abdominal respiration continued, but became much slower. The fall of blood pressure after the initial injection of a dose of 0.06 cc. per kilo was 32 per cent in one case. In another experiment in which 0.085 cc. per kilo was given blood pressure fell 45 per cent.

The increasing effects of oil of chenopodium on the circulation and respiration observed after repeated doses (figs. 10 and 12) failed to manifest themselves, however, in some cases. As shown in Cat No. 320, respiration was not affected either by the sixth or seventh injection, while the blood pressure fell 10 mm. or 11 per cent as a result of the seventh injection.

Cat 287. Weight, 1600 grams. Ether anesthesia

First injection at 2.07 p.m. of 3.2 cc. (0.04 cc. per kilo), 2 per cent emulsion of oil of chenopodium. Injected in 30 seconds. Blood pressure fell from 125 mm. to 115 mm. Hg, or 8 per cent. Recovered in 5 minutes. Abdominal respiration decreased in amplitude fully one-third, while thoracic respiration also became very superficial. The rate decreased from 20 to 6 per minute. Considerable improvement took place during the next 5 minutes, but recovery was incomplete at this time.

Second injection at 2.12 p.m. 3 cc. of 2 per cent emulsion of oil of chenopodium were injected in 60 seconds. Blood pressure fell from 120 to 90 mm. Hg, or 25 per cent, and remained at this level for about 2½ minutes. The rate of cardiac action was also appreciably decreased. Recovered 7 minutes after injection. Thoracic respiration stopped immediately after injection and began to recover slowly two minutes later. Abdominal respiration became slower after injection but improvement began within one and a half minutes.

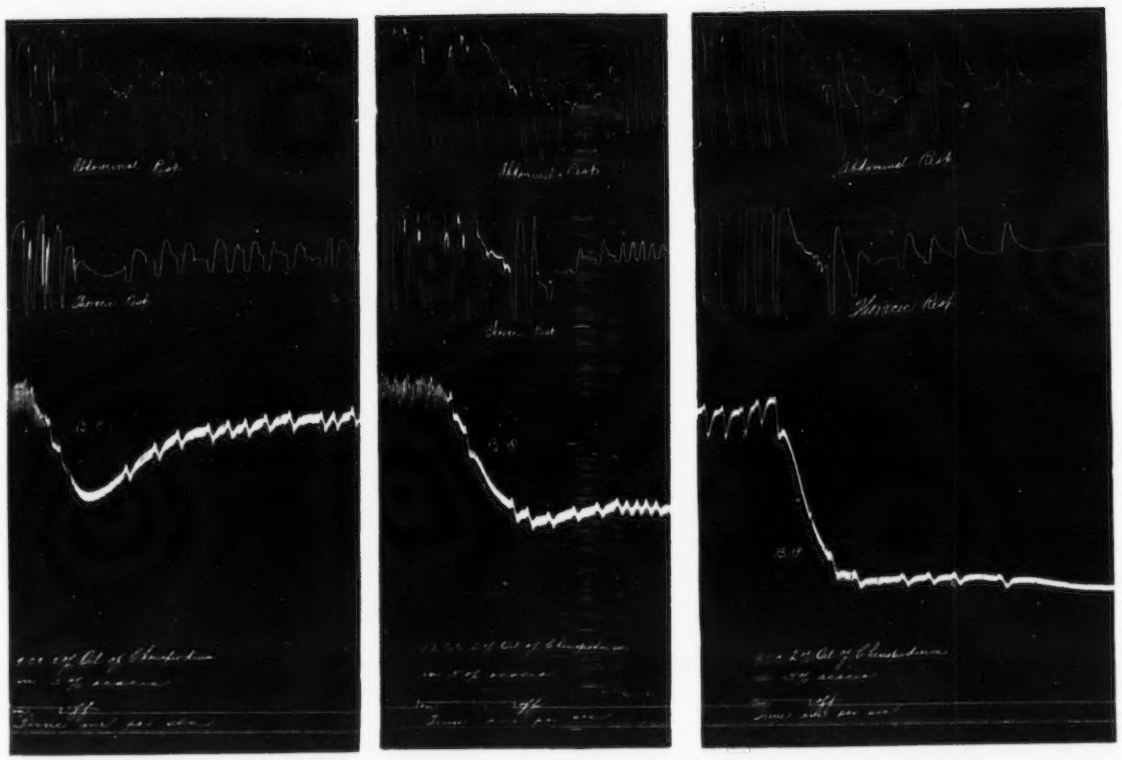
Third injection at 2.19 p.m. Blood pressure 120 mm. Hg. Three cc. of emulsion of oil of chenopodium were injected in 40 seconds. Blood pressure equals 95 mm. Hg. Frequency of respiration decreased 50 per cent, thoracic respiration disappeared. Abdominal respiration markedly decreased. Note cumulative effect on respiration.

Cat 300, female. Weight, 3080 grams. Well fed

December 4, 1914. Ether anesthesia.

1.45 p.m. Received 18 cc. 5 per cent cocoanut oil emulsion in acacia in 2 minutes. Slight rise of blood pressure.

1.58 p.m. Central end of left vagus stimulated for 5 seconds, the right vagus being intact. Distance of P. from S. coil 8 cm. Marked fall of blood pressure and slowing of the heart. Respiration stimulated.



Cat 300. Showing effect on respiration and circulation after the injection of chenopodium.

Fig. 10. 0.06 cc. per kilo.

Fig. 11. 0.08 cc. per kilo, 8 minutes after first injection.

Fig. 12. 0.06 cc. per kilo, 23 minutes after second injection.

2.07 p.m. Central end of left vagus stimulated. Distance P. from S. coil 16 cm. Slight fall of blood pressure. Respiration slowed.

2.08 p.m. 9 cc. 2 per cent oil of chenopodium given in 5 per cent emulsion of acacia. Blood pressure fell from 185 to 125 mm., or 32 per cent. Respiration stopped for about 20 seconds, then returned, but was much slower than before. Amplitude of thoracic respiration was much more depressed than abdominal.

2.12 p.m. Blood pressure recovered. Central end of vagus stimulated 5 seconds. Distance of P. from S. coil 8 cm. No effect on blood pressure but respiration distinctly stimulated.

2.16 p.m. 12 cc. 2 per cent emulsion oil of chenopodium given in 5 per cent acacia and cocoanut oil. Blood pressure fell from 190 to 110 mm., or about 42 per cent. Respiration stopped for about 20 seconds then returned but was much slower. Thoracic respiration very feeble, abdominal respiration slower than before injection but depth not markedly less than before. While blood pressure remained low, 18 cc. of an emulsion of 5 per cent cocoanut oil in 5 per cent acacia were injected at the rate of 12 cc. per minute. Blood pressure rose gradually from 105 to 140 mm. in 40 seconds but there was no noticeable improvement in respiration. Respiration, on the contrary, became much slower. Almost immediately after injection of cocoanut oil emulsion, blood pressure fell about 40 per cent; respiration became irregular, then slow. Another injection of 12 cc. 5 per cent cocoanut oil emulsion was made in 70 seconds; blood pressure steadily rose from 60 mm. to 150 mm. Hg in half a minute. Respiration became deeper and more frequent toward the end of the injection, but this lasted half a minute and stopped altogether.

2.39 p.m., or 16 minutes later, the injection of 9 cc. of 2 per cent oil of chenopodium in 20 seconds caused a sudden drop of blood pressure from 170 to 70 mm., respiration becoming slow.

2.41 p.m. No improvement in blood pressure. Respiration became slower than before. Eighteen cc. cocoanut oil were injected; blood pressure became still slower, respiration stimulated at first, then stopped. Animal dead.

Cat 286. Weight, 2740 grams

1.43 p.m. 12 cc. (0.087 cc. per kilo) emulsion of 2 per cent oil of chenopodium injected in 70 seconds. Blood pressure fell from 145 to 80 mm. Hg, or 45 per cent, by the time the injection was completed. Two minutes later no change in blood pressure. Respiration much slower, thoracic respiration became very superficial, abdominal respiration deeper, but much slower than before injection. Ten minutes later blood pressure was 130 mm. Hg. Respiration was much improved but did not return to normal.

Second injection was made of 12 cc. 2 per cent emulsion of oil of chenopodium. Blood pressure fell from 130 to 60 mm. Hg by the end of the injection, 100 seconds. Effect on respiration was very marked; abdominal respiration less depressed than thoracic. Forty-five seconds after injection respiration stopped, blood pressure was but a few mm. Hg, heart continued to beat 40 seconds after respiration stopped.

Cat 320. Weight 3.3 kilos

3.15 p.m. Injected 7 cc. 1 per cent oil of chenopodium in 50 seconds. Blood pressure before injection was 160 mm. after injection 150 mm. Respiration became much slower, amplitude was decreased.

3.19 p.m. Blood pressure was 160 mm. Hg. Injected 7 cc. oil of chenopodium in 53 seconds. Blood pressure was 145. Blood pressure began to rise at once; at 3.23 p.m. the blood pressure was 160 mm. Hg. Injected 15 cc. 1 per cent oil of chenopodium in 5 minutes.

3.28 p.m. Blood pressure was 140 mm. Hg. Recovered in 3 minutes.

3.31 p.m. Blood pressure was 160 mm. Hg.

3.33 p.m. Injected 13 cc. 1 per cent oil of chenopodium in 1¾ minutes. Blood pressure before injection was 155 mm. Hg. At the end of the injection blood pressure was 125 mm. No change in 3 minutes, then rose gradually. Respiration decreased in force and frequency.

3.49 p.m. Blood pressure was 145 mm. Hg. 13 cc. 1 per cent oil of chenopodium injected in 72 seconds. Blood pressure before injection was 145 mm. Hg at the end of the injection 100 mm. Hg, which continued without change 6 minutes before recovery began. Respiration was much slower and weaker. Thoracic respiration just perceptible; abdominal respiration regular and fairly strong, but weaker than before injection.

4.15 p.m. Blood pressure 110 mm. Hg. Injected 13 cc. 1 per cent oil of chenopodium in 3½ minutes. Blood pressure 80 mm. Hg. Respiration remained unchanged.

4.28 p.m. Blood pressure 90 mm. Hg, injected 13 cc. 1 per cent oil of chenopodium in 1½ minutes. Blood pressure 80 mm. Hg. No change in respiration.

4.34 p.m. Blood pressure 70 mm. Hg. Injected 30 cc. 1 per cent oil of chenopodium in 3½ minutes, At the end of injection blood pressure began to decline rapidly and reached zero in about one minute. Respiration stopped before heart action was arrested. A few respiratory movements noticed after heart stopped.

EXPERIMENTS ON RABBITS.

The circulatory changes produced by chenopodium as observed in rabbits, under ether or urethane anesthesia, indicate that even a small dose may produce considerable depression. Blood pressure fell 16 to 20 per cent after initial doses of 0.022 to 0.027 cc. oil of chenopodium per kilo were injected intravenously (fig. 13). The rate of injection was about 7 cc. per minute, in some experiments, while the time occupied in other experiments was about 5 seconds for the introduction of the entire amount. Te fall of blood pressure was usually prompt, but it began to rise almost immediately, often within 30 seconds from the time the lowest level was attained. Recovery was accomplished in some experiments in 3 to 5 minutes, in others the process occupied more than double this time. Larger doses may be more active though this was not always the case. In two experiments with 0.04 and 0.08 cc. oil of chenopodium per kilo the effect of the initial injection did not

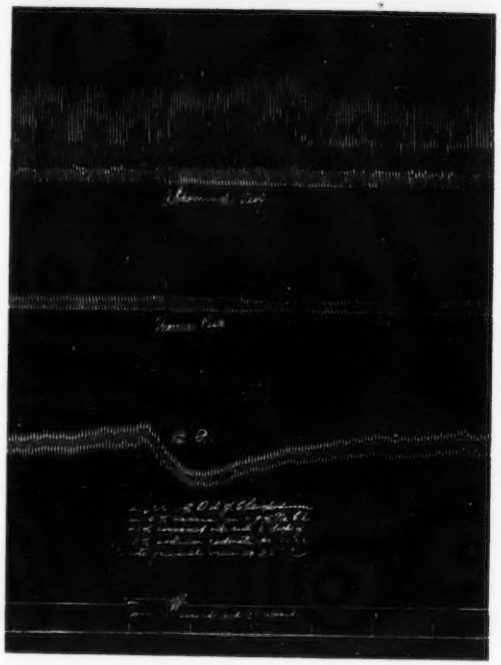


Fig. 13. Rabbit 1763. Showing fall of blood pressure and stimulation of respiration after 0.02 cc. chenopodium per kilo.

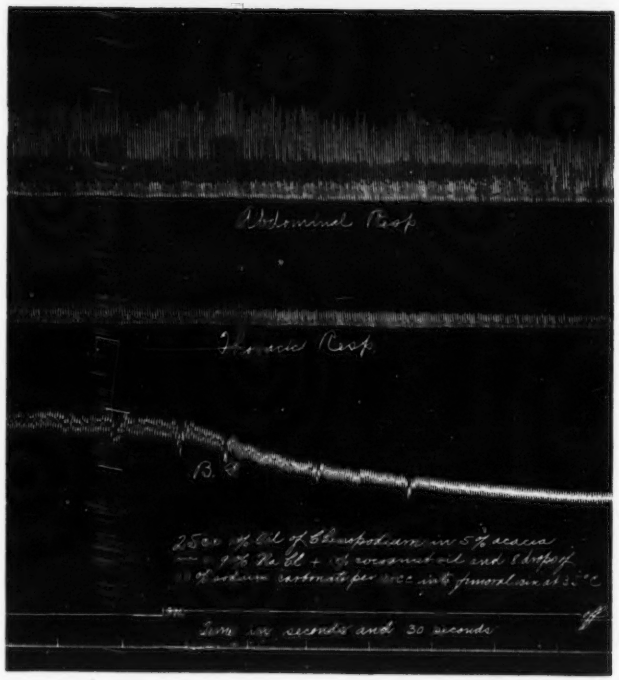


Fig. 14. Rabbit 1772. The intravenous injection of 0.08 cc. chenopodium per kilo shows marked fall of blood pressure and moderate decrease of respiratory amplitude.

differ from that of smaller doses. But this is in all probability exceptional as the results were different when the experiments were repeated in other rabbits. The initial injection of 0.08 cc. of oil of chenopodium per kilo (fig. 14) produced a fall of blood pressure amounting to 45 mm. Hg or 39 per cent in one experiment. The relative effect of subsequent injections did not differ appreciably from that produced by the initial dose. This was observed after experiments with small as well as with larger doses, and may be readily seen from the following abbreviated protocols.

Rabbit 1772. Gray female. Weight 3.19 kilos.
March 8, 1915. Received 6 grams urethane by mouth through stomach tube.

	EMULSION OF 1 PER CENT CHENOPODIUM INJECTED	BLOOD PRESSURE		FALL OF BLOOD PRESSURE		DURATION OF INJECTION
		Before injection	After injection	mm. Hg	Per cent	
	cc.					
1.08	25.0	115	70	45	39	3 min. 20 sec.
1.41	25.0	90	58	32	35	4 min. 5 sec.
2.19	25.0	65	35	30	46	2 min. 40 sec.
2.54	20.0					2 min. 50 sec.

NOTE: Blood pressure gradually fell and rabbit died at 3.01 p.m.

Rabbit 1763. Gray male. Weight 2.3 kilos.
March 3, 10.30. Received by mouth through stomach tube, 2.5 grams urethane.

12.01	4.6	95	75	20	21	20 sec.
12.15	5.0	105	80	25	24	36 sec.
12.30	5.0	102	85	17	16	43 sec.
12.40	5.0	100	85	15	15	90 sec.
12.46	10.0	100	70	30	30	70 sec.

Rabbit 1718. Weight 2.2 kilos. Ether anesthesia.
6 cc. control solution injected—no effect.

	EMULSION OF 1 PER CENT CHENOPODIUM INJECTED	BLOOD PRESSURE		FALL OF BLOOD PRESSURE		DURATION OF INJECTION
		Before injection	After injection	mm. Hg	Per cent	
	cc.					
1.55	6.0	118	95	23	20	55 sec.
2.03	6.0	110	84	26	23.6	
2.19	5.5	125	96	29	23+	1 min.
2.30	5.0	106	94	12	11+	1 min.
2.48	6.0	85	65	20	23+	75 sec.

A progressive increase in the fall of blood pressure was observed, however, in some experiments after chenopodium. A second injection of the same amount as the first was twice as effective, while a third injection was approximately three times as active as the initial dose, the amounts introduced each time being the same. The absolute and relative fall of blood pressure are shown in the following table:

	1696 0.08 cc.	1660 0.02 cc.	1702 0.027 cc.	1661 0.04 cc.
1	20 mm. or 23 per cent	25 mm. or 18 per cent	15 mm. or 16 per cent	22 mm. or 20 per cent
2	32 mm. or 46 per cent	45 mm. or 37 per cent	30 mm. or 36 per cent	28 mm. or 28 per cent
3		50 mm. or 50 per cent	40 mm. or 50 per cent	35 mm. or 35 per cent
Remarks	Died after receiving 0.16 per kilo.	Died after receiving 0.083 per kilo.	Died after receiving 0.08 cc. per kilo.	Died after receiving 0.24 cc. per kilo.

It may be remarked that the fatal dose in the experiments presented in this table was considerably smaller than in those rabbits in which no cumulative effect on the circulation could be demonstrated. The acute fatal dose of chenopodium when administered intravenously varied in our experiments between 0.3 and 0.35 cc. per kilo and in one instance it was 0.48 cc. per kilo. The results obtained in Rabbit 1661 in which the effect of repeated injections were much less marked than in the other three rabbits given in the table suggest that the resistance to chenopodium might be a factor in determining cumulation. It may be of interest in this connection to call attention to the condition of the heart in Rabbit 1660. Post mortem examination indicated the presence of serious damage to the myocardium, brought about possibly by repeated bleeding extending over a period of several weeks which were made by thrusting a hypodermic needle into the organ. Although this case does not afford sufficient evidence for any positive statement regarding the relation of the condition of the heart to circulatory disturbance caused by chenopodium, it is nevertheless suggestive and may perhaps account for similar effects observed in other experiments.

As shown in the experiments cited below, cumulation was likewise indicated when larger doses of chenopodium were injected after considerable quantities had previously been introduced into the circulation. Perhaps also in these cases the increased action was due to damage of the heart caused by the previous treatment with chenopodium.

Rabbit 1709. Weight, 2275 grams

No previous injection.
35 cc. 1 per cent chenopodium injected in 8 minutes.
Blood pressure fell from 100 to 80 mm. Hg, or 20 per cent.

Rabbit 1681. White male. Weight, 2250 grams.

Total quantity previously injected 0.25 cc.
Seven minutes later 22.5 cc. 1 per cent chenopodium injected in 15 minutes.
Blood pressure fell from 88 mm. before injection to 40 mm. or 54 per cent when injection was discontinued.

Rabbit 1718. Weight, 2.2 kilos.

Total quantity of chenopodium injected 0.4 cc, or 0.18 cc. per kilo; 5 minutes after last injection 22.5 cc. 1 per cent emulsion of oil of chenopodium injected in 8½ minutes.
Blood pressure fell from 85 mm. to 40 mm. Hg, or 52 per cent.

The action of chenopodium on respiration was in several respects different from its effects on the circulation. The initial injection of small and moderate doses, the duration of which varied from 5 to 60 seconds, did not produce any respiratory changes in most experiments. In some cases slight, in others transitory but well marked stimulation was observed, even when the initial dose was large (fig. 13). A dose of 0.08 cc. per kilo produced in one rabbit (1772, fig. 14) a moderate decrease of amplitude, while in another it caused a slight depression only. The rate of injection in this case was 4.5 cc. 1 per cent emulsion of oil of chenopodium per minute. Subsequent injections of large doses were much more active, but the case was different when smaller amounts were administered. A second or third injection of a small dose which was not previously effective sometimes produced respiratory depression but this was not always the case. In one experiment a number of injections were made without affecting respiration; only after the fifth injection when 0.05 cc. per kilo at one dose was given the total amount previously received being 0.1 cc. per kilo, was any effect noticed in this experiment, thoracic respiration being markedly depressed but abdominal respiration remained unchanged. Similar results were obtained in another experiment (1681). In this case two doses, each of 0.022 cc. per kilo, produced a slight increase of amplitude. In the third the amplitude of thoracic respiration decreased 33 per cent after a dose of 0.066 cc. per kilo. No change in abdominal respiration was observed. Another injection of 0.1 cc. per kilo begun 7 minutes later and carried out in 15 minutes, produced a still greater

effect on thoracic respiration, the amplitude being decreased 65 per cent, but abdominal respiration remained unchanged. In neither test was the rate affected.

Although the amount required to depress respiration varied a good deal in different individuals, it may be safely stated that when a sufficient amount was introduced into the circulation, respiration became decidedly weaker, amplitude, as well as the rate being decreased. It may be pointed out, however, that the frequency of respiration was but moderately depressed. This was also observed in rabbits in which stimulation occurred at first. Although respiration seemed to be less affected by chenopodium than the circulation, arrest of respiration usually took place either at the same time or before heart action ceased. In several experiments in which the heart was exposed it was found beating feebly and continued some time in this condition—15 minutes to one hour.

DISCUSSION.

A survey of the results obtained in the foregoing experiments shows that the effect of oil of chenopodium on different animals is essentially the same notwithstanding the occasional departure from the general type of action and the marked quantitative differences produced in the same animals under changed conditions of experimentation. This was illustrated by the characteristic action on the circulation and respiration and also by the resistance to chenopodium as indicated by the amounts tolerated, which varied in rabbits between 0.15 cc. and 0.48 cc per kilo, being in most cases between 0.3 cc. and 0.35 cc. While the largest amounts in dogs were 0.47 cc., the smallest was 0.3 per cc. per kilo. Cats succumbed when the total quantities reached 0.2 to 0.36 cc. per kilo. The average is, therefore, approximately the same in all the animals examined. Intravenous injections were usually followed by circulatory and respiratory disturbances. The initial dose produced a fall of blood pressure in dogs, cats, and rabbits but the action when this was repeated was greater in the dog and rabbit than in the cat. The effect on dogs was markedly enhanced, the fall of blood pressure being several times greater when chloretone anesthesia was substituted for morphine and ether. The action in different animals varied still more when the injections were repeated. Thus the failure of the circulation to react after a large amount of chenopodium has been introduced in divided dose, which was frequently observed in dogs, was seldom seen in the cat and was absent in rabbits.

That chenopodium is a respiratory depressant was abundantly shown in our experiments but the behavior of different animals in this respect likewise presented interesting differences. Respiratory depression after the same amounts in proportion to body weight was more marked in cats than in dogs. In rabbits, it will be recalled, small doses may produce stimulation at first, depression having been noticed only after the dose was repeated several times. Besides, apnoea was seldom observed in rabbits even after large doses. Bruning's (6) experiments on the behavior of the red blood cells toward chenopodium are of interest in this connection since he found that hemolysis and methemoglobin may be produced in vitro. It is conceivable that disturbance of respiration may be caused by the hemolytic action and the formation of methemoglobin. We have, therefore, carried out a number of observations with the oil of chenopodium to determine whether methemoglobin and hemolysis may be produced in vivo. Doses of 0.02 cc. to 0.24 cc. per kilo were injected intravenously. A spectroscopic examination of the blood obtained from animals thus treated failed to indicate the presence of methemoglobin. Hemolysis was also absent even after large amounts were administered. This was studied in cats after the introduction of two grams per kilo of the oil into the stomach or small intestine, and in rabbits which received 0.1 to 0.16 cc. per kilo intravenously. A moderate degree of hemolytic action was present in dogs' blood taken after oil of chenopodium was injected intravenously and kept at low temperature for 24 hours, but this was about the same in degree which may be observed when blood is obtained from anesthetized dogs that have not received oil of chenopodium. Depression of the circulation may also be thought of as a factor in determining the respiratory changes observed, but the results obtained in a large proportion of our experiments do not support this view. As shown in figure 2, blood pressure fell about 40 per cent but respiration was only slightly depressed. On the other hand, respiratory depression was observed when the circulation no longer reacted to chenopodium. Moreover, in experiments on rabbits a fall of blood pressure and a coincident stimulation of respiration often occurred.

Paralysis or depression of the vagus may also be thought of in this connection as a possible cause, but some of our observations with chenopodium were made on dogs and cats in which both vagi were cut. As the characterisfic effect on respiration was present in both these animals it would seem that the action was central. It is evident that no satisfactory explanation of the respiratory effect can be offered at

present. The work of Loevenhart and Grove (7) is, however, suggestive. After the intravenous injection of the salts of iodoso and iodoxy benzoic acid, the effects on respiration which these investigators observed were strikingly similar to those of chenopodium. They believed that the apnoea was due to the liberation of oxygen in the blood by these substances. As shown by Nelson (8) and later by Wallach (9), ascaridole, which is the active principle in the oil of chenopodium, is a peroxide. Although it does not oxidize guaiac, it is quite possible that its action in vivo may be similar to that of the salts of benzoic acid. The depression of respiration and apnoea may be due, therefore, to the oxygen liberated by ascaridole. This explanation does not seem to apply to the action of oil of chenopodium in the rabbit, but may, indeed, contradict it. That this is not the case, however, appears when the relative amounts of carbon dioxide and oxygen in the blood of different animals, which formed the subjects of our experiments, are taken into consideration. According to Heinz (10), the carbon dioxide, as compared with the oxygen, in the blood of the rabbit, is relatively greater than in the dog or cat. Since carbon dioxide stimulates respiration, according to Henderson (11) and others, its action would be antagonistic to that of oil of chenopodium, thus tending to neutralize the effect produced by the liberation of oxygen. The relatively greater amount of carbon dioxide in the blood of the rabbit would, therefore, prevent the onset of respiratory depression and apnoea. This may also explain the difference in the final stages of intoxication. The simultaneous failure of the circulation and respiration frequently observed in chenopodium poisoning in the rabbit is probably due to direct action on the heart, since respiration is impaired but not abolished. Cardiac asphyxia (Henderson, l. c.), such as would occur in the dog or cat on account of prolonged apnoea is not probable in the rabbit, there being enough oxygen to sustain heart action while the respiration goes on, though very much diminished. Finally the anesthesia produced by chenopodium may also be considered as a factor in the production of apnoea and respiratory depression. According to Henderson the respiratory center is much less sensitive to carbon dioxide in profound anesthesia, but the evidence obtained does not favor this explanation as in profound anesthesia, such as was produced by chloretone and alcohol, the administration of chenopodium, according to this explanation, should have produced apnoea much more readily than when the same was given in morphine-ether anesthesia.

SUMMARY

1. The intravenous injection of doses of 0.02 to 0.085 cc. of chenopodium per kilo produced a fall of blood pressure in dogs, cats and rabbits. Recovery was observed.

2. The effect was greater in dogs than in rabbits or cats.

3. A second injection of the same dose produced a greater effect, but when this injection was repeated until the total amount reached about 0.2 cc. per kilo, no response of the circulation could be observed. This was especially the case in dogs, but to a much smaller extent in cats. This phenomenon was absent in rabbits.

4. Fall of blood pressure was of cardiac origin, as the volume of the kidney decreased with the fall of blood pressure.

5. Frequency of heart action was diminished after oil of chenopodium.

6. A very marked decrease of vagus irritability was observed after oil of chenopodium.

7. Respiratory depression such as decreased amplitude and rate, with apnoea, was also caused by chenopodium, but the effect with small doses was less constant than on the circulation.

8. Cats react more readily than dogs.

9. Small doses may stimulate respiration in rabbits. Apnoea was very seldom observed in the rabbit, even after large doses.

10. No methemoglobin or hemolysis was observed even after the intravenous injection of 0.02 to 0.024 cc. per kilo, or the introduction of two grams per kilo into the stomach or small intestine of the cat.

11. Liberation of oxygen in the body by ascaridole is suggested as a possible cause of respiratory depression and apnoea.

12. Action of chenopodium on respiration is independent of its effect on the circulation.

13. Reduction of sensitiveness of respiratory center to carbon dioxide is not the cause of action of chenopodium on respiration.

14. Amounts of chenopodium tolerated by intravenous injection varied in the same animals. The average is approximately 0.03 to 0.35 cc. per kilo in dog, cat and rabbit.

15. The less depressant action of chenopodium on respiration in the rabbit is attributed to relatively larger amounts of carbon dioxide in the blood.

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INFLUENCE OF DIIODOTYROSINE AND IODOTHYRINE ON THE SECRETION OF CEREBROSPINAL FLUID

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In a previous communication we have shown that thyroid extract slows the rate of secretion of cerebrospinal fluid. The present work was undertaken to discover, if possible, what constituent of the thyroid gland possesses the power of inhibiting the cerebrospinal fluid secretion. In this paper we present the results of experiments with iodothyrine, a commercial derivative of the thyroid gland, and of diiodotyrosine, a synthetic substance closely related to the iodine complex of the thyroid gland. The diiodotyrosine was prepared and kindly furnished for these experiments by Dr. Treat B. Johnson of Yale University.

The anesthesia, rate of secretion of cerebrospinal fluid, and the blood pressure records were obtained with the technique described in a previous paper (1).

Diiodotyrosine. The injection of solutions of this substance into the femoral vein causes no change in blood pressure or in respirations, so that all changes in the outflow of cerebrospinal fluid which result from the injection may be considered as due to the effect of the substance on the secretion of the choroid plexus.

The results of four experiments with diiodotyrosine are given in the table on next page.

Experiment I. The injection of 0.1 gm. of diiodotyrosine intravenously causes a marked decrease in the flow of cerebrospinal fluid. This is pronounced even in the first half hour after injection, the flow dropping from the normal 3.78 cc. to 1.28 cc., a decrease in rate of secretion of 0.0833 cc. per minute. The flow of cerebrospinal fluid gradually grows less to the end of the experiment, two and one-half hours after the injection, although slightly more fluid escapes in the last period than in the two preceding it. The average flow for the five 30-minute periods after injection is only 0.8 cc., a decrease from the normal flow of 2.98 cc. The normal rate of secretion is 0.126 cc. per minute, while

the average rate for the five periods is 0.026 cc. per minute, a decrease in rate of secretion of cerebrospinal fluid after the injection of 0.1 gm. of diiodotyrosine of 0.1 cc. per minute.

Experiment II. The injection of 0.2 gm. of diiodotyrosine in this instance does not show as pronounced an effect on the amount of secretion in the first half hour as was noted with 0.1 gm. in Experiment I. The flow is lessened, however, and steadily decreases after the second period. The flow for the first half hour is 1.28 cc. against 1.59 cc. for the normal period. This is a decrease in rate of secretion from 0.053 cc. per minute to 0.042 cc. per minute. The flow for the second period

Diiodotyrosine

PERIODS	FLOW IN CC. OF C. S. F. FOR 30-MINUTE PERIODS			
	Experiment I. 0.1 gm. injec.	Experiment II. 0.2 gm. injec.	Experiment III. 0.2 gm. injec.	Experiment IV. 0.1 gm. injec.
Before injection	3.78	1.59	2.82	1.62
After injection 1	1.28	1.28	1.63	1.28
2	0.99	1.39	0.66	1.29
3	0.56	1.23	0.77	1.23
4	0.51	0.88	0.78	0.88
5	0.67	0.47	0.28	0.47
6		0.11		0.11
7		0.26		0.26
Average flow for 30 minutes.	0.80	0.80	0.82	0.78
Decrease from normal	2.98	0.79	2.00	0.84

is larger than that for the first, but decreases below the first in the third period.

The flow then rapidly lessens till in the sixth period only 0.11 cc. is secreted an average rate of 0.003 cc. per minute. The flow in the seventh period is somewhat more rapid than in the preceding 30 minutes, but still has a rate of only 0.008 cc. per minute. The average flow for 30 minutes for the seven periods (three and one-half hours) is 0.8 cc. a decrease of 0.79 cc. from the normal flow. This is a decrease in secretory rate of 0.027 cc. per minute.

Experiment III. The injection of 0.2 gm. of diiodotyrosine in another dog gives more pronounced results than in Experiment II. In this experiment the reduction in flow is pronounced in the first half hour with a further marked drop in the second period, while in the third and fourth the flow is practically uniform. The decrease in

flow for the first period is 1.19 cc., a reduction of 0.04 cc. per minute in rate of outflow. The second period shows a decrease from the first period of 0.97 cc. or a reduction in rate of outflow of 0.032 cc. per minute. The third and fourth periods have a slightly greater flow than the second, 0.77 cc. and 0.78 cc. respectively against 0.66 cc. for the second. The fifth period, however, is much slower, only 0.28 cc. escaping in the 30 minutes. The average 30-minute flow for the five periods is 0.82 cc., a decrease from the normal of 2 cc. or a reduction in rate of 0.067 cc. per minute.

Experiment IV. The injection of 0.1 gm. of diiodotyrosine in this experiment gives less striking results than in Experiment I. In fact the results are very similar to those of Experiment II in which twice the amount was injected. The decrease in flow is noticeable in the first half-hour and remains practically the same for the first hour and a half after injection. It then rapidly decreases for one and a half hours, with a slight increase in the last half-hour. The flow in the first period decreases 0.34 cc. from the normal, or a decrease in rate of secretion of 0.011 cc. per minute. The flow is then practically unchanged until the fourth period when 0.88 cc. escapes in 30 minutes. The fifth and sixth periods show reductions to 0.47 cc. and 0.11 cc. respectively. The seventh or final period shows a slight increase to 0.26 cc. The average flow for 30 minutes for the seven periods is 0.78 cc., a decrease from the normal amount of 0.84 cc. or a decrease in rate of secretion of 0.028 cc. per minute.

It is evident from the above experiments that diiodotyrosine in solution when injected intravenously has an inhibitory action on the secretion of the choroid plexus very similar to that of saline extracts of the thyroid gland. The results on different dogs are not uniform, but seem to depend somewhat upon the normal rate of cerebrospinal fluid secretion.

Iodothyrine. The intravenous injections of iodothyrine solution produce no changes in blood pressure or respiration. The results of four injections are given in the table on next page.

Experiment I. The injection of 0.3 gm. iodothyrine gives a decrease of 0.32 cc. cerebrospinal fluid for the first half hour, a decrease in rate of 0.11 cc. per minute. The flow shows a steady reduction which in the fifth and sixth periods has decreased to 0.4 cc., a decrease from normal of 0.95 cc. The average 30-minute flow for the six periods is 0.66 cc. a drop from normal of 0.69 cc. or a decrease of 0.023 cc. per minute in rate of secretion.

Experiment II. The injection of 0.05 gm. iodothyrine has very little influence on the flow of cerebrospinal fluid.

The flow in the half hour before injection is 1.41 cc. and in the first period after injection is 1.10 cc., a reduction of 0.31 cc. or a decrease in rate of 0.11 cc. per minute. However, in the second period the flow returns to normal. In the succeeding two periods it again decreases, the average 30-minute flow for the four periods after injection is 1.15 cc., a decrease of only 0.26 cc. or in rate of only 0.009 cc. per minute. This is almost within the range of the normal decrease.

Experiment III. In this experiment 0.5 gm. iodothyrine gives very little change in the first half hour, the decrease only amounting to 0.09

Iodothyrine

PERIODS	FLOW IN CC. OF C. S. F. FOR 30-MINUTE PERIODS			
	Experiment I. 0.3 gm. injec.	Experiment II. 0.05 gm. injec.	Experiment III. 0.5 gm. injec.	Experiment IV. 0.3 gm. injec.
Before injection	1.35	1.41	1.74	2.97
After injection 1	1.03	1.10	1.65	1.41
2	0.92	1.40	1.17*	0.57
3	0.73	1.23	0.63	0.11
4	0.53	0.90		
5	0.40			
6	0.40			
Average flow for 30 minutes	0.66	1.15	1.15	0.69
Decrease from normal	0.69	0.26	0.59	2.28

* 1.5 gm. injected.

cc., a second injection (1.5 gm.) is then given and the next period shows a more marked reduction. This response reduced the flow 0.57 cc. below the normal. The third period shows a further reduction from normal of 1.11 cc. Owing to an unavoidable accident the experiment was terminated at this point. The average 30-minute flow for the periods after injection is 1.15 cc., a decrease of 0.59 cc. or a drop from the normal rate of 0.058 cc. per minute to 0.038 cc. per minute.

Experiment IV. The injection of 0.3 gm. iodothyrine in another dog gives a more marked decrease than in any of the three previous experiments. The reduction in the first half hour after injection is pronounced, slightly less than half the normal amount of fluid flowing from the cannula. The actual decrease in this period is 1.56 cc. The flow in the third period is slightly larger than in the second, while in

the third it is again greatly reduced. The average flow for a 30-minute period after injection is 0.69 cc., a drop below the normal of 2.28 cc. or a decrease in secretion rate from 0.099 cc. per minute to 0.023 cc. per minute, a reduction of 0.076 cc. per minute.

The experiments with iodothyrine tend to show that small amounts, such as 0.05 gm. have very little influence on the rate of secretion of cerebrospinal fluid. Larger amounts result in a slower rate, but with the exception of Experiment IV, the decrease is not as marked as that produced by diiodotyrosine or saline extracts of thyroid gland.

It is evident from the experiments, both with diiodotyrosine and iodothyrine, that different dogs react very differently to the same amount of substance. As a general rule the most marked responses are in those animals which have normally a very rapid secretion. Sex and age gave apparently no influence, while the weight of the animal seems to make very little difference.

Control experiments have shown that the decrease in flow noted in the above experiments is due to the action on the choroid plexus of the substance injected. A decrease does occur normally, but this is so slight as to be negligible in the two to four hours which are considered in these experiments.

CONCLUSIONS

1. The intravenous injection of diiodotyrosine has an inhibitory influence on the rate of secretion of the choroid plexus. This decrease in rate usually appears in the first half hour after injection, but is not so marked as that obtained with saline extracts of fresh thyroid gland.

2. Iodothyrine in solution, injected intravenously, has little influence on the rate of cerebrospinal fluid secretion when given in small amounts (0.05 gm.). In amounts of 0.3 gm. and 0.5 gm. there is some inhibition of the rate of choroid plexus secretion, but not as marked as that produced by diiodotyrosine or saline extracts of fresh thyroid.

THE RESPONSE OF THE VASODILATOR MECHANISM TO WEAK, INTERMEDIATE, AND STRONG SENSORY STIMULATION

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In the study of vasomotor reflexes the desirability has long been recognized of supplementing by means of plethysmographic studies of individual organs the information gained from observations of blood-pressure changes. Recently Tschalussow[1] has described a method of employing the nasal cavity as a plethysmograph, and has found it to be of exceptional delicacy.

In certain studies from this laboratory the characteristic depressor effect of *weak* sensory stimulation has been emphasized,[2] and it has seemed to us worth while to supplement these studies with observations of the effects of weak sensory stimuli on the volume of the nasal cavity.

METHOD

Our experiments were performed on cats. In some cases urethane anesthesia was employed; in others rapid decerebration under ether was performed. The method of preparing the nasal cavity was the modification of Tschalussow's original one described by one of us.[3] Simultaneous blood-pressure records were made from a femoral artery. For sensory stimulation electrodes (Sherrington type) were placed centrally on branches of the brachial and sciatic trunks, and in some experiments on the vagus or saphenous. Induction shocks of known intensity (Z units[4]) were used for excitation. The rate varied between 5 and 15 per second.

[1] Tschalussow: Archiv für die gesammte Physiologie, cli, 1913, 524.

[2] Martin and Lacey: This Journal, xxxiii, 1914, 212; Martin and Stiles: ibid xxxiv, 1914, 106.

[3] Mendenhall: This Journal, xxxvi, 1914, 58.

[4] Martin: The measurement of induction shocks, New York, 1912, 73.

The nasal cavity is peculiarly adapted for an analysis of depressor reflexes, since it receives both vasodilator and vasoconstrictor fibres,[5] and can respond, therefore, to reflex influences acting either through the vasoconstrictor or the vasodilator central mechanism.

With our method of recording nasal volume-change, as in the experiments of Tschalussow (loc. cit), an up-stroke of the lever signifies vasodilation, and a down stroke vasoconstriction. Changes in nasal volume following stimulation of sensory nerves can be interpreted as signifying particular vasomotor effects only when recorded in connection with simultaneous records of general blood pressure, for only thus can passive changes be distinguished from active ones. Even when so accompanied, the distinction cannot always be made with certainty. To be sure, active nasal vasoconstriction occurring simultaneously with general vasoconstriction is readily distinguished, since here we have a down-stroke of the nasal recorder with upward movement of the blood-pressure tracing; likewise active nasal vasodilation in the presence of general vasodilation presents no difficulty since in this case there will be an upward stroke of the nasal recorder with downward movement of the blood-pressure tracing. The difficulty arises when we attempt to determine whether local active vasomotor changes may occur in the presence of general vasomotor changes of opposite sign. To determine whether the nasal vessels are actively dilating or are merely being gorged passively by rising general blood pressure requires the most careful analysis of the records.

For purposes of comparison we have found it desirable, as did Tschalussow,[6] to bring about known passive changes in nasal circulation. Means to this end are compression of the abdominal aorta, which brings about passive engorgement of the vessels of the head; or compression of the thorax, or peripheral stimulation of the cut vagus to cause the blood supply to the head to be lessened. In our experience the nasal cavity always responds immediately to these procedures. Tschalussow found (loc. cit., 52), that the nasal vessels react to passive engorgement by energetic local contraction. This we have seen in a few, but by no means in all, of our experiments. As an index of passive engorgement, therefore, we do not consider this after contraction wholly reliable.

Observations. In general the nasal volume changes brought about by stimulation of sensory nerves correspond with expectation. That is

[5] Langley: Philosophical Transactions, London, clxxxiii, 85; Dastre and Morat: Recherches sur le systeme nerveux vaso-moteur, Paris, 1884, 115 et seq.

[6] Tschalussow: Loc. cit., 527.

to say, weak stimuli, such as cause drop in general blood pressure, cause simultaneously nasal vasodilation, and strong stimuli, which cause a rise of pressure, produce nasal vasoconstriction. The nasal mucosa, therefore shares actively in the reactions by which both pressure-fall and pressure-rise come about.

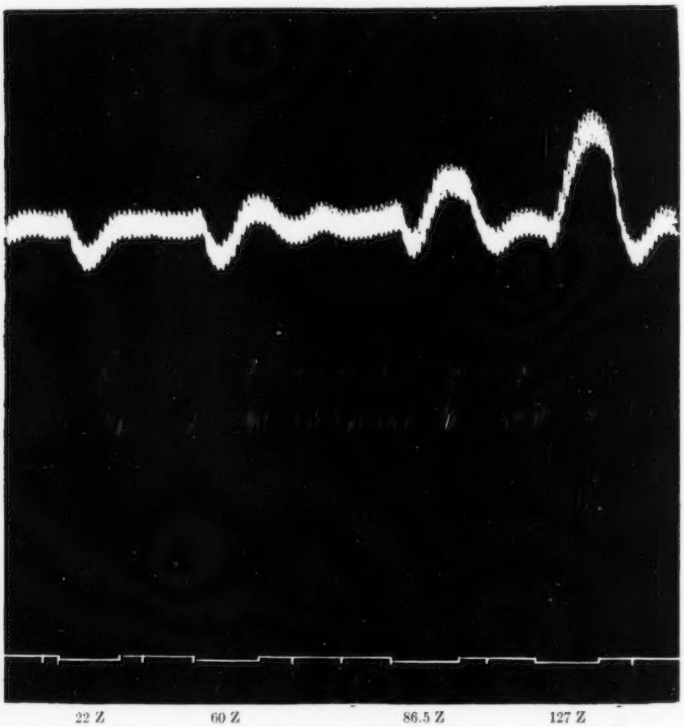

Fig. 1. The transition from a depressor to a pressor response with increasing strength of stimulation. The time signal is at the line of zero-pressure. Time in 30 second intervals. Stimulation strengths in Z units. Peroneal nerve stimulated.

In the presence of a mechanism of this sort, in which weak stimulation produces one sort of response and strong stimulation of precisely the same nerve trunks a diametrically opposite response, a degree of interest naturally centres about the point of reversal, for here, at the

point where one sort of influence relinquishes control of the mechanism to another sort, we may hope to gain some insight into the nature and mode of action of the influences themselves. The great sensitiveness of the nasal plethysmograph lends itself to this possibility.

So far as we are aware the character of the blood-pressure curve under sensory stimulation near the reversal point has not hitherto been reported in detail, although it has been observed in this laboratory from the beginning of our quantitative study of vaso-motor reflexes, and has undoubtedly been observed incidentally by other investigators. A typical example of the transition from a depressor to a pressor reflex is presented in figure 1. As the strength of sensory stimulation is increased above that which brings about pure pressure-drop a tendency develops toward the replacement, during the period of stimulation, of the initial pressure-drop by a pressure-rise. This tendency becomes more and more marked, until, in most cases, with the application of sufficiently strong stimulation, the initial depressor phase is completely suppressed, leaving the rise of pressure as the only visible response. In the particular experiment illustrated in the figure the region of reversal occurred with somewhat weaker stimulations than we have ordinarily found adequate. The average of all our experiments places the "reversal thresholds" in the neighborhood of 200–250 Z units as compared with 60–90 in this experiment.

Fig. 2. Active nasal vasodilation persisting throughout a vasomotor reflex consisting of a depressor followed by a pressor phase. Peroneal nerve stimulated.

The responses of the nasal plethysmograph to sensory stimulation in the region of "reversal" are instructive. During the initial pressure drop there is active dilation of the nasal mucosa. As the depressor phase is succeeded by the pressor there is often a corresponding change to active constriction of the nasal vessels. This latter reaction is not, however, invariable. We have sometimes seen the active nasal dilation persist throughout the pressor phase, particularly when the latter was not very pronounced. Such a case is illustrated in figure 2. In this same experiment stronger stimulation brought about a typical pressor reaction with the usual active nasal constriction.

A further suggestive observation is that in a fair percentage of cases of ordinary pressor stimulation active constriction of the nasal mucosa does not begin at the instant o pressure-rise but several seconds thereafter. The latent period for the nasal mucosa, where a well marked one occurs, averages about 15 seconds. Obviously the discharge of the vasoconstrictor centre which brings about the pressure-rise does not, in these cases, involve immediately the nasal mucosa. A simple explanation would be that in this region, which is also under the control of the vasodilator mechanism, active vasoconstriction is held in abeyance for a time by a simultaneous vasodilator discharge.

From all these observations we may draw the inference that depressor influences and pressor influences can be aroused simultaneously by suitable stimulation of individual sensory nerve trunks, and that the resultant effect on the peripheral vasomotor mechanism depends on the balance that is established between the opposing influences. To put the point in other words, when strong sensory stimulation brings about a rise in blood pressure, it may be that depressor influences are not suppressed, but merely overpowered.

In any attempt to analyze the interaction of simultaneous pressor and depressor influences we have to bear in mind the potentially twofold nature of each. Pressor influences may act positively on the vasoconstrictor centre or negatively on the vasodilator, either separately, or, as Bayliss maintains,[7] on both together. Likewise depressor influences may operate either through lowering constrictor tone or heightening dilator tone or both. A method of separating these factors used by Bayliss (loc. cit.), and also by Fofanow and Tschalussow,[8] consists in cutting either the constrictor or the dilator efferent paths to the organ upon which plethysmographic studies are being made. By this means observed vasomotor changes can be assigned definitely to one or the other mechanism. We have applied this method in our experiments with the nasal plethysmograph in order to determine whether the depressor influences manifested during weak sensory stimulation involve activity of the vasodilator mechanism. We find that marked active nasal dilation is induced by weak stimulation when both cervical sympathetic nerves are severed. This procedure cuts the nasal mucosa off from its connection with the vasoconstrictor centre while leaving it in communication with the dilator mechanism through the

[7] Bayliss: Proceedings of the Royal Society of London, 1908, lxxx, B, 339.

[8] Fofanow and Tschalussow: Archiv für die gesammte Physiologie, cli, 1913, 543.

Vidian nerves.[9] The observed dilation is the result, therefore, of positive discharges through the vasodilator system.

By the same procedure we have attempted to show whether the depressor influences which we have pictured above as present but ineffective during strong sensory stimulation involve posit ve action of the vasodilator mechanism. We have repeated the observations of Fofanow and Tschalussow on the effects on the nasal mucosa of stimulating the vago-depressor trunk[10] and confirm their finding that strong stimulation of this trunk with both cervical sympathetics cut brings about active reflex vasodilation, indicating a positive action upon the vasodilator apparatus.

The attempt to demonstrate by this method activity of the vasodilator mechanism during ordinary pressor stimulation is rendered difficult by the circumstance that when the cervical sympathetic nerves are cut the nasal mucosa may respond passively to the general rise of blood pressure, giving, as already pointed out, a tracing that is difficult to distinguish from active vasodilation.

There are two features, however, in which active dilation may differ from passive. The first is in time relationships, the second in degree of response.

A passive nasal volume-change must necessarily *synchronize accurately* with the blood-pressure rise or fall which produces it. The *degree* of response, moreover, will show some relation to the amount of general pressure-change, unless, indeed, the local reaction described by Tschalussow occurs (loc. cit., 52), in which case the response is immediately identified thereby as a passive one. In an experiment in which both cervical sympathetics are cut, a nasal dilation during pressor stimulation, which definitely outlasts the general pressure rise; or a series of dilations of *equal* extent in connection with pressor responses of *different* amounts, indicate strongly, if they do not prove conclusively, that the dilator mechanism is active during strong stimulation of sensory nerves. Both these appearances we have encountered in the course of our work, and they have been sufficiently clean cut to satisfy us that they were not accidental. For example, in one experiment, strong sensory stimulation (900 Z units) applied for 30 seconds, caused a reflex rise of pressure which fatigued quickly; so that the pressure had returned to the original level 5 seconds before the period of stimulation was over. Well marked nasal dilation accompanied the response

[9] Tschalussow: Loc. cit., 539.

[10] Fofanow and Tschalussow: Loc. cit., 554.

and continued for four seconds after stimulation ceased, outlasting the period of heightened pressure a total of 9 seconds. In another experiment, one with an exceptionally low pressor threshold, sensory stimulation of 35 Z units caused a rise of pressure of 14 per cent, and stimulation on the same nerve of 127 Z units caused a rise of pressure of 29 per cent. The nasal dilation was slightly more pronounced in the first case than in the second. The mechanical limit of the nasal mucosa was not approached either time, for compression of the abdominal aorta, within 9 minutes of these observations, produced a passive nasal dilation nearly double the greater of them.

DISCUSSION

On the basis of the observations reported above, and those formerly reported from this laboratory we would suggest the following as a possible picture of the responses of the vasomotor mechanism to sensory stimulations of increasing strength. Weak sensory stimuli excite the vasodilator apparatus to activity. The result is a drop in general blood pressure, with active dilation in such organs as are provided with vasodilator nerves. Our data yield no positive information as to whether weak stimuli affect the vasoconstrictor centre; but if this centre is affected appreciably it is inhibited. As stronger and stronger sensory stimuli are used there begins to develop, concurrently with the active vasodilation, excitation of the vasoconstrictor centre. The latter is more potent than the concomitant dilation although its latency appears to be ordinarily somewhat longer, for the typical response to intermediate stimulation is an initial active dilation followed by, and overpowered by, a subsequent active constriction. With still stronger stimuli the active constriction develops with less delay, so that, save in exceptional cases, no indication is afforded of the vasodilator discharges which are occurring simultaneously with the predominant vasoconstrictor activity. When the sensory nerve stimulated is the vagodepressor trunk, the situation is the same, except that with this nerve strong stimulation inhibits the vasoconstrictor centre, reinforcing, instead of opposing, the concurrent dilator discharges.

This suggestion of concurrent excitation of both mechanisms is directly contrary to the view of Bayliss (loc. cit.), according to which vasoconstrictor excitation is accompanied by inhibition of vasodilator tone. Bayliss states that most of his attempts to demonstrate inhibition of dilator tone gave negative results.[11] He reports, however, two

[11] Bayliss: Loc. cit., 349.

experiments which he interprets as supporting his contention (loc. cit., 350). In the first of these, during a pressor reflex with rising general blood pressure, active vasoconstriction occurred in the ear of a rabbit both of whose cervical sympathetics had been cut. Since virtually all vasoconstrictor fibres were presumably severed Bayliss considers that this active vasoconstriction was brought about through inhibition of vasodilator tone. This interpretation involves the rather difficult mechanical conception that the arterioles are so forcibly held open through their dilator innervation that when this innervation subsides they will constrict forcibly against a rising blood pressure in the complete absence of constrictor excitation. The alternative possibility suggests itself that in this particular animal an aberrant vasoconstrictor innervation to the ears was present. As supporting this alternative we wish to cite an experiment of our own. On February 26, 1915, we were making observations on a cat under urethane anesthesia. After eliciting typical pressor responses from stimulation of the left peroneal and left radial nerves, with active nasal vasoconstrictions with each response, we cut both cervical sympathetics and repeated the sensory stimulations. Contrary to our experience in numerous other experiments, and to our great surprise, each pressor reflex was accompanied, precisely as before, by active nasal vasoconstriction instead of by the ex-

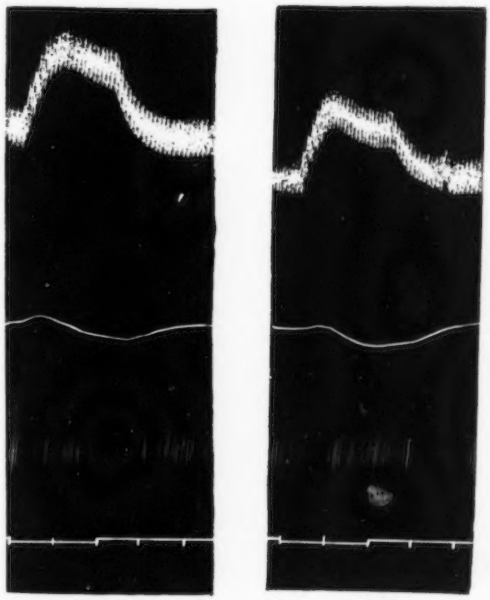

Fig. 3. Active nasal vasoconstriction during pressor stimulation. *a*, cervical sympathetics intact; *b*, cervical sympathetics cut. Peroneal nerve stimulated.

pected dilation. We performed ten sensory stimulations, three on the left radial, four on the left peroneal, and three on the left popliteal with results as stated. Figure 3 gives two tracings from this experiment. In both of these the stimulation was applied to the peroneal; the strength of stimulus was 1300 Z. Stimulation *a* shows the response before the cervical sympathetics were cut; *b*, the response after they were cut. The interval between stimulations *a* and *b* was 12 minutes. The cervical sympathetics were cut 5 minutes after stimulation *a*. The animal was vagotomized, and we searched both carotid sheaths carefully for minute nerve strands that might represent portions of the cervical sympathetics separate from the main trunks. Comparison of the nasal tracings in *a* and *b* of the figure indicates strongly that if the first represents vasoconstrictor excitation the second does also. We consider aberrant vasoconstrictor innervation a much more probable explanation of this and of Bayliss' phenomenon than depression of dilator tone.

Bayliss' second experiment is one in which diminution of volume of the hind leg occurred in an animal, presumably with abdominal sympathetics cut, from stimulation of the median nerve, with simultaneous excitation of the depressor and the peripheral end of the cervical sympathetic. The conditions of stimulation in this experiment are such as to make the interpretation of the results difficult. An investigation now in progress in this laboratory on the effects of simultaneous stimulation of the depressor and other sensory nerves reveals a complexity of interaction requiring careful quantitative comparisons for analysis. The results of this investigation will be reported in due course. In this connection we wish to say only that we should hesitate to admit the possibility of inhibition of vasodilator tone during adequate stimulation of the depressor nerve, unless all other possibilities, such as aberrant vasoconstrictor innervation, or passive redistribution of blood, were more rigorously excluded than they appear to have been in this experiment.

SUMMARY

Depressor (weak) stimulation of sensory nerves produces active dilation of the vessels of the nasal mucosa.

Pressor (strong) sensory stimulation produces active constriction in the nasal mucosa.

Sensory stimuli of intermediate intensity produce typically an initial fall in general blood pressure followed by a rise. The nasal mucosa

shows active dilation during the initial depressor period. Sometimes the dilation persists through the second or pressor phase; at other times there is active nasal constriction during the pressor phase.

In many instances the active constriction of the nasal mucosa under pressor stimulation shows a longer latency than does the general blood pressure rise.

Both these observations suggest an active dilator influence which is able for a time to oppose successfully the constrictor influence occurring simultaneously.

When both cervical sympathetic nerves are cut weak sensory stimulation produces active dilation of the vessels of the nasal mucosa, showing that the vasodilator mechanism is excited by weak stimuli.

We confirm the observation of Fofanow and Tschalussow that with strong stimulation of the vago-depressor trunk, when the cervical sympathetics are cut, the vasodilator mechanism is excited.

Observations are reported which indicate that the nasal dilation seen when strong (pressor) stimulation is applied to ordinary sensory nerves, with both cervical sympathetics cut, is, in part, at least, the result of excitation of the vasodilator mechanism.

On the basis of these experiments the suggestion is made that the vasodilator apparatus is ordinarily excited whenever sensory nerve trunks are adequately stimulated. Strong stimuli, by exciting concurrently the vasoconstrictor mechanism, may overpower the dilation in regions where both innervations obtain.

Although this suggestion is based altogether upon the results of artificial stimulation of sensory nerve trunks and contains no implication that *receptor* stimulation may not be selective as regards the elicitation of vasodilator or vasoconstrictor responses independently, it may not be amiss to point out that an important feature of the physiological significance of the high blood pressure induced by vasoconstriction is in the diversion of much of the blood of the body into those organs which appear to have a vasodilator innervation but no constrictor, namely, the skeletal muscles. This distribution of the blood would be favored by the mechanism here postulated.

SPINAL ANAESTHESIA IN THE CAT

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The dangers and discomforts of ether anaesthesia have long been recognized. Inevitable nausea, possible pneumonia, difficult respiration, renal injuries, make ether anaesthesia impossible in certain cases, dangerous in others, and distressing in all. To meet these difficulties, spinal anaesthesia was devised for use in fields where general anaesthesia is superfluous, such as operations on the perineum. As a rule beneficent, spinal anaesthesia is nevertheless by exception open to a grave and sudden danger. In the course of surgical procedures otherwise completely successful, the vasomotor apparatus may suddenly give way. The fall in blood pressure is immediate, sometimes profound, always disquieting. Nor can the surgeon predict in what patient it may appear.

The points of interest in this phenomenon are as follows: (1) The extent and the time relations of the fall in blood pressure and the effect of this fall on the efficiency of the central nervous system. (2) The region paralyzed. (3) The structures affected, whether the vasomotor center, the roots of the spinal nerves, the afferent or the efferent paths in the body of the spinal cord. (4) The extent to which the drug may pass along the cord from the point of injection, as modified by the per cent of the drug in the solution used, the bulk of this solution, the force of gravity, and the possible fixation of the drug by the tissues which it bathes. (5) The duration of the phenomena. (6) The influence of adrenalin. (7) Remedial measures, directed to raising the fallen blood pressure.

Obviously, these factors cannot be studied with complete satisfaction in man, in whom the condition of experimentation cannot be varied at will. We present, therefore, a systematic investigation of spinal anaesthesia in animals.[1]

[1] The only experimental study of blood pressure in spinal anaesthesia so far as we are aware, is that of Gray and Parsons (Quarterly Journal of Medicine, 1911, v, p. 339), who concluded that the slight fall of blood pressure they obtained in all cases was due to relaxation of the muscles of the abdomen and the lower limbs and that the greater fall obtained in some cases was due to paralysis of the intercostal muscles and the consequent diminution in the pumping power of the chest.

METHOD

Fifty cats were used. In a number of these, two or more intraspinal injections were made, so that, in all, 72 experiments were done. In 18 cases, ether alone was used. In all the animals, the preliminary operations were done under ether anaesthesia. In 32 cases, in which muscular reactions would have been a vital source of error, ether was followed by curare. Enough dilute curare solution to paralyze the skeletal muscles was slowly injected through the femoral vein. The carotid blood pressure was recorded by a membrane manometer. Graduation scales for this manometer are shown in figures 1, 2 and 3. The condition of the vasomotor system and of the sensory afferent tracts was determined by measuring the changes in blood pressure on stimulation of the central end of the brachial and sciatic nerves and on stimulation of the dorsal columns of the cord. The induction currents employed were just perceptible to the tongue. In order to make sure that the drug entered the subdural space, the injection was made under the guidance of the eye. Laminectomy, therefore, was always done at the level of the injection. To determine the spread of the drug by direct stimulation of the cord, laminectomy was often done at other levels as well. A 2 cc. all-glass Luer syringe with 24 gauge needle was used. In the cat, the space between the cord and the dura is so shallow that, except in the lower lumbar region, the needle cannot be inserted perpendicularly to the long axis of the cord without impaling the cord itself. The direction of the needle, whether pointing cephalad or caudad, was found to be a factor of some influence on determining the level to which the drug diffused.

In most of the experiments undertaken to ascertain the effect of gravity, the foot of the board was raised.

In 35 injections, tablets "C" containing 0.05 g. novocaine and 0.000083 g. adrenalin were used; in 18 injections, tablets "D" containing 0.2 g. novocaine and 0.06 g. sodium chloride; in 17 injections, a fluid preparation put up in ampoules, each of which contained 1.3 cc. of 5 per cent tropacocaine and 0.00017 g. suprarenin chloride; and in 2 injections, a fluid preparation in ampoules containing 1 cc. of 5 per cent tropacocaine in 0.6 per cent sodium chloride solution. Taking as a test the paralysis of the tissue directly bathed by the drug when injected, the novocaine with adrenalin gave 28 per cent unsatisfactory results, ranging from partial to complete failure; novocaine and salt, 38 per cent; tropacocaine and adrenalin, 23 per cent; only two injections were made with tropacocaine and salt and both

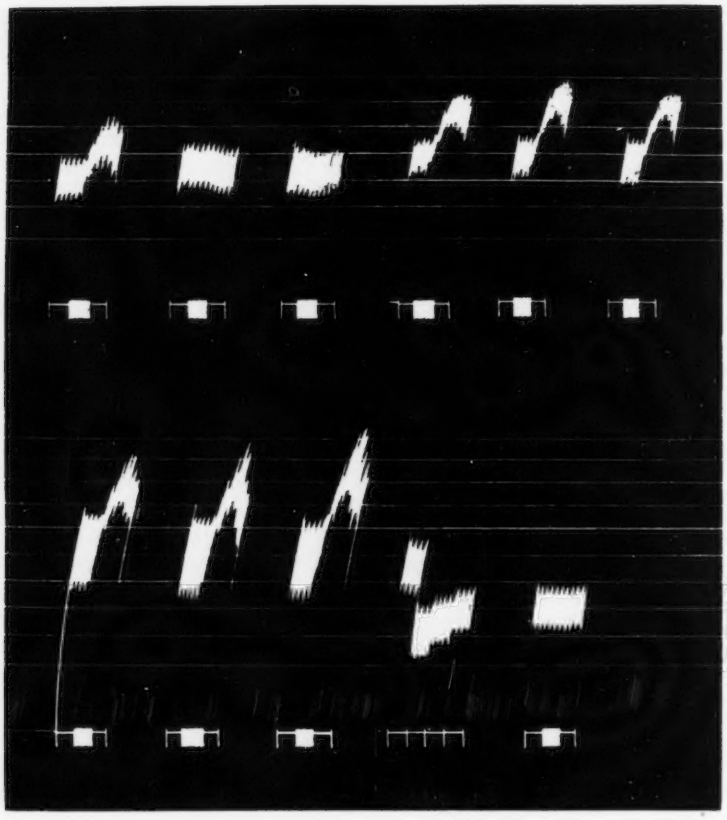

Fig. 1. The original size. Injection of 0.01 g. novocaine and adrenalin in dilute solution (1 cc.) at Lumbar VII causes paralysis of dorsal columns extending to Dorsal XI, and perhaps above. Brachial rise reduced from 65 to 33 per cent.

Lower curve—left to right		*Upper curve—left to right*	
1. Sciatic stimulation	12.10 p.m.	1. Brachial stimulation	12.35 p.m.
2. Brachial stimulation	12.14	2. Lumbar VII stimulation	12.37
3. Lumbar VII stimulation	12.15	3. Dorsal XI stimulation	12.39
4. Record of blood pressure	12.17	4. Sciatic stimulation	3.25
	(12.22 Injection of drug)	5. Lumbar VII stimulation	3.27
	12.25	6. Dorsal XI Stimulation	3.29
	12.28		
	12.31		
5. Sciatic stimulation	12.32		

Scale: 50, 70, 90, 110, 130, 150, mm. Hg.

Experiment 45, curarized cat. February 26, 1915.

were successful. The percentages of failure were considerably higher than in the clinical use of the same drugs, a difference probably due to the conditions obtaining in experimental work on so small an animal, and to the use of inadequate doses in certain experiments.

Following is a typical protocol.

Experiment February 26, 1915. A lightly etherized cat was tracheotomized and cannulas placed in the left carotid artery and the left femoral vein. The left brachial and sciatic nerves were tied and cut distal to the ligature. Laminectomy was done at Lumbar VII and Dorsal XI. The carotid cannula was connected with a membrane manometer.

11.50 a.m. 1.2 cc. 0.5 per cent curare solution in 15 cc. normal saline solution injected into femoral vein.[2] Artificial respiration.

12.10 p.m. Sciatic nerve stimulated with induction currents. The blood pressure rose from 105 mm. to 170 mm. Hg. (see fig. 1). Stimulation of brachial nerve and of dorsal columns at Lumbar VII gave slightly greater increase.

12.17. Blood pressure recorded.

12.22. 1.0 cc. of 1.0 per cent novocaine and adrenalin C (made with distilled water) was injected very slowly into the dural sac at Lumbar VII. The needle was inserted perpendicularly to the long axis of the cord.

12.25. Blood pressure has fallen from 100 mm. to 55 mm.

12.28. Blood pressure 65 mm.

12.31. Blood pressure 71 mm.

12.32. Stimulation of sciatic nerve. The reflex change in blood pressure has disappeared.

12.35. Brachial stimulation causes a rise from 75 to 100 mm. (33 per cent) instead of the rise from 100 mm. to 165 mm. (65 per cent) shown before novocaine.

12.37. No reflex rise on stimulating cord at Lumbar VII

12.39. No reflex rise on stimulating cord at Dorsal XI.

3.25. Stimulation of sciatic, brachial, Lumbar VII, and Dorsal XI cause normal reflex increase in blood pressure.

In all the experiments, especial care was taken to avoid errors from ether, curare, and artificial respiration.[3]

CHANGES IN BLOOD PRESSURE

Extent of fall. In Table 1 are recorded 20 experiments in which novocaine or tropacocaine was injected in the lumbar region in strength sufficient to block all afferent impulses set up by stimulation of the sciatic nerve. In two cases, the blood pressure fell more than 40 per cent. A fall of 40 per cent is, however, not necessarily alarming.

[2] This small dose of curare is excreted after artificial respiration has continued some time and the curare must then be renewed.

[3] For precautions, see W. T. Porter: this Journal, 1910, xxvii, pp. 281, 282.

TABLE 1

NO.	SITE OF INJECTION	BLOOD PRESSURE	ABSOLUTE FALL	PERCENTILE FALL
	Lumbar	*from to*		
12	I	138–105	33	24
20	III	100– 90	10	10
25	VI	150-100	50	33
26	VII	130–100	30	23
28	VII	140–130	10	7
29	VII	100	0	0
30	VII	130–140		
31	VII	80– 70	10	12
32	VII	120–100	20	8
33	VII	170–140	30	18
34	VII	130-120	10	8
39	VII	90	0	0
40	VII	100– 80	20	20
42	VII	120– 95	20	17
44	VII	160–100	60	38
45	VII	100– 55	45	45
47	VII	100– 70	30	30
48	VII	150– 80	70	47
49	VI	120– 90	30	25
50	VII	190–170	20	11
	Dorsal			
2	XIII	120– 80	40	33
3	IX	130– 80	50	38
4	II	115– 30	85	74
5	IV	120– 75	45	38
6	IV	100– 40	60	60
7	IV	100– 40	60	60
8	IV	120– 75	45	38
9	IV	100– 90	30	30
13	I	110– 60	50	45
21	II	120– 40	80	67
22	X	130– 60	70	53
26	XII	115– 80	35	30
27	XII	80– 50	30	38
29	XI	100– 90	10	10
32	XII	120– 75	45	38
34	X	120– 30	90	75
35	IX	110– 80	30	27
37	XI	80– 70	10	13
43	VI	110– 45	60	55
	Cervical			
14	III	125– 70	55	44
15	III	100– 80	20	20
16	III	90– 60	30	33
17	III	95– 40	55	58
18	III	80– 60	20	25
19	IV —	120– 80	40	33
23	III	80– 55	25	31
36	III	110–160		
36	III	100– 60	40	40
38	III	110–100	10	9
38	III	120–110	10	8
38	III	100– 90	10	10
46	II	130– 70	60	46

The criterion is not the absolute or percentile fall of blood pressure per se, but whether there remains sufficient blood pressure to carry on, for a time at least, the work of nerve cells in the brain and cord. In one of the two cases just cited, the pressure fell from 150 mm. to 80 mm. Hg, in the other it fell from 100 mm. to 55 mm. The danger line may probably be placed at 60 mm. In only one instance out of twenty, therefore, was there a serious fall in consequence of a lumbar injection.

In the dorsal region, 19 injections were made, in 9 of which the blood pressure fell to 60 or less.

In the cervical region, there were 13 injections and in 5 the blood pressure fell to 60 or below.

In the cat the residual blood pressure, after the extirpation of the spinal cord[4] is from 28 to 31 mm. In our present experiments, the lowest blood pressure after lumbar injection was 55 (one instance); after dorsal injection, the pressure fell in two cats to 30 mm. and in three cats to 40 mm.; after cervical injection, the pressure fell once to 40 mm. In several instances, therefore, the vasomotor apparatus was absolutely paralyzed and the function lost as completely as if the spinal cord had been extirpated. These instances were, in each case, the result of injection in the dorsal or cervical regions.

Duration of low blood pressure. The injury to nerve cells caused by low blood pressure and the consequent impaired nutrition, depends on two variables; namely, the extent to which the pressure falls and the duration of the low pressure. Recovery from the slight falls in blood pressure usually took place rapidly. After the more severe falls, partial but sufficient recovery took place in from 30 to 90 minutes. The duration of low blood pressure appeared to depend more upon the amount of drug injected than upon the site of injection.

Our experiments give evidence that in the majority of instances the vasomotor system was not seriously impaired by the pressures noted in Table I. After 70 to 180 minutes the reflex change in blood pressure on stimulation of the sciatic and brachial nerves returned almost, if not quite, to normal. Thus in Experiment 43, sciatic stimulation caused the blood pressure to rise from 90 to 145 mm., 61 per cent. After injection at Dorsal VI, the pressure fell from 110 to 45 mm. Seventy minutes later, the blood pressure was 70 mm. and on sciatic stimulation it rose to 110 mm., 57 per cent.

[4] Porter and Storey: this Journal, 1907, xviii, p. 196.

THE REGION PARALYZED

It is obvious that drugs like novocaine, which are given to interrupt the afferent conducting paths in the spinal cord, may also interrupt the efferent paths. The object in view is to suspend sensations of pain without at the same time suspending some function essential to the well-being of the patient. Such injuries must depend on the importance of the several regions paralyzed. Reflection upon the anatomy of the spinal cord will show that the vasomotor and the respiratory functions are especially to be considered.

The vasomotor function. The reader is reminded that the master cells controlling the tonus of the arteries and thus the weight of the blood pressure are situated in the bulb. Their axis cylinder processes descend the cord in the antero-lateral tracts, bend into the gray matter, and end there in contact with the spinal vasomotor cells. The axis cylinder processes of the spinal vasomotor cells leave the cord in the anterior roots of spinal nerves from the first Dorsal to about the first Sacral. The vascular areas served by these fibers are most of them without importance in the present investigation. Thus in the cat, the sciatic nerve, bearing vasomotor fibers for the hind limb, may be severed without causing any considerable fall in blood pressure. In fact, only the splanchnic nerves, given off from the upper dorsal region, innervate a vascular area large enough to be a dangerous factor in spinal anaesthesia. This area, comprising the abdominal viscera, is, however, so extensive as to make splanchnic paralysis very serious, in that the dilatation of the arteries controlled by the splanchnic vasomotor fibers may cause so much blood to enter the corresponding veins that not enough is left in the bulb and cord to support properly respiration and other vital functions. The rabbit, for example, may be bled to death into its own portal system, by section of the splanchnic nerves. In studying the regions affected by spinal anaesthesia, special attention should, therefore, be paid to that containing the splanchnic fibers. Spinal anaesthesia can be successful, only when the afferent paths are paralyzed without at the same time paralyzing enough splanchnic cells or splanchnic root fibers to lower the blood pressure to a degree that may threaten the continued activity of the centers situated in the cervical cord and the bulb.

The importance of the splanchnic area becomes clear when attention is directed to the average percentile fall in blood pressure after injections in the several regions of the cord (Table 1). The averages are: lumbar, 19 per cent; dorsal, 43 per cent; and cervical 27 per cent.

The regional averages just presented, show that the fall in blood pressure, following dorsal injection, is due to paralysis in the splanchnic region and not to paralysis of the bulbar vasomotor center. For, if the fall were due to interference with the bulbar center or with the vasomotor fibers connecting it with the spinal vasomotor cells, the use of novocaine in the cervical region, nearer the bulbar center, should

TABLE 2

Maximum fall in blood pressure in relation to dosage, region injected, and direction of injection

Fall of 30 Per Cent or Less						Fall of More Than 30 Per Cent					
EXPERIMENT NO.	BULK	PER CENT	LEVEL	NEEDLE TOWARDS	PER CENT FALL	EXPERIMENT NO.	BULK	PER CENT	LEVEL	NEEDLE TOWARDS	PER CENT FALL
	cc.						*cc.*				
17	0.2	4	C. III	Head	5	46	0.2	5	C. II	Head	46
18	0.3	4	C. III	Head	18	16	0.4	2	C. III	Tail	33
						4	0.4	2.5	D. II	Tail	73
9	0.1	1	D. IV	Head	10	8	0.1	1	D. IV	Tail	37
35	0.4	2.5	D. IX	Spine	27	5	0.3	2	D. IV	Tail	37
12	0.5	2	L. I	Tail	24	7	0.1	2	D. IV	Tail	60
11	0.4	2	L. II	Tail	24	6	0.2	2	D. IV	Tail	60
10	0.2	2	L. III	Head	25	43	0.2	5	D. VI	Spine	54
49	0.2	5	L. VI	Spine	25	3	0.5	2	D. IX	Head	38
47	0.5	2	L. VII	Head injected forcibly.	30	2	0.5	1	D. XIII	Head	33
42	0.2	5	L. VII	Spine	16	25	0.2	2.5	L. VI		33
50	0.2	10	L. VII	Spine	10	44	1.0	1.5	L. VII	Spine	37
						45	1.0	1.0	L. VII	Spine	45
						48	0.8	2.5	L. VII	Spine	47

In all the above experiments a mixture of novocaine and adrenalin C. was used.
"Spine" means that the needle was pointed at right angles to the long axis of the cord.

SUMMARY

	Injection away from splanchnic area 11 *Experiments*	*Injection in splanchnic area* 14 *Experiments*
Average dose	= 0.0093 g.	= 0.0082 g.
Average bulk	= 0.3 cc.	= 0.42 cc.
Average per cent	= 3.6 per cent	= 2.3 per cent
Average blood pressure fall	= 19.5 per cent	= 45.2 per cent

cause as great a fall as its use in the dorsal region—at any rate, the fall should not be less.

The conclusion that the vasomotor paralyses of spinal anaesthesia are to be sought in the splanchnic area rather than in the bulbar vasomotor center is further supported by the observations on the fall of blood pressure as affected by the direction in which the injection is made.

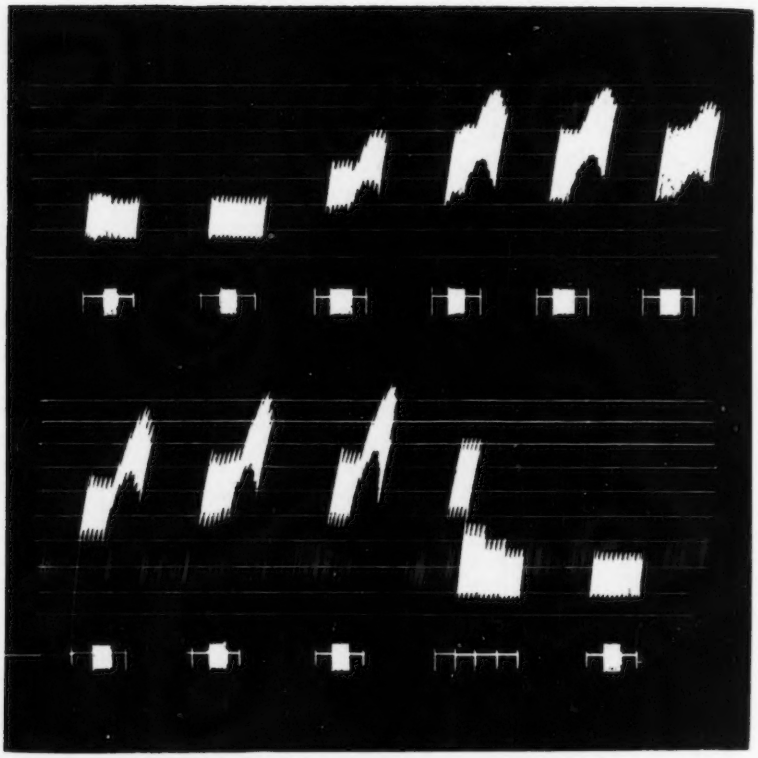

Fig. 2. The original size. Injection of 0.01 g. novocaine and adrenalin (0.2 cc.) at Dorsal VI causes fall in blood pressure from 110 mm. to 45 mm. in three minutes with abolition of vasomotor reflex from sciatic and brachial.

Lower curve—left to right		*Upper curve—left to right*	
1. Sciatic stimulation	8.55 p.m.	1. Brachial stimulation	9.15 p.m.
2. Brachial stimulation	8.58	2. Dorsal VI stimulation	9.17
3. Dorsal VI stimulation	9.01	3. Brachial stimulation	9.42
4. Record of blood pressure	9.02	4. Brachial stimulation	10.12
	(9.03 Injection of drug)	5. Sciatic stimulation	10.14
	9.06	6. Dorsal VI stimulation	10.15
	9.09		
	9.12		
5. Sciatic stimulation	9.13		

Scale: 30, 50, 70, 90, 110 ,130, 150, mm. Hg.
Experiment 43, curarized cat. February 19, 1915.

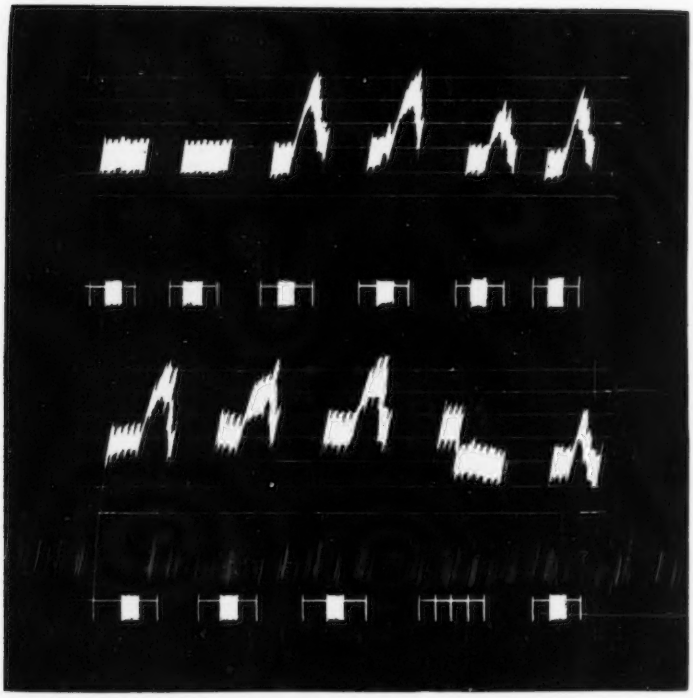

Fig. 3. The original size. Injection of 0.01 g. novocaine and adrenalin (0.2 cc.) at Lumbar VII causes fall of blood pressure from 120 mm. to 95 mm. in three minutes. Paralysis of sciatic incomplete eleven minutes after injection. Elevation of foot of board at angle of 30°, eighteen minutes after injection, is followed by complete paralysis of sciatic nerve.

Lower curve—left to right		*Upper curve—left to right*	
1. Sciatic stimulation	9.11 p.m.	1. Sciatic stimulation	9.48 p.m.
2. Brachial stimulation	9.13	2. Lumbar VII stimulation	9.49
3. Lumbar VII stimulation	9.15	3. Lumbar I stimulation	9.51
4. Record of blood pressure	9.17	4. Brachial stimulation	9.54
	(9.22 Injection of drug)	5. Sciatic Stimulation	10.22
	9.25		
	9.28		
	9.31		
5. Sciatic stimulation	9.33		

Scale: 70, 90, 110, 130, 150, 170, 190 mm. Hg.

Experiment 42, curarized cat. February 16, 1915.

Table 2 deals with the fall of blood pressure in relation to dosage, region injected, and the direction of the injection. On the left side of this table are placed the cases in which the fall of blood pressure was 30 per cent or less; on the right side are those in which the fall was more than 30 per cent of the initial pressure. In every case in which the fall was 30 per cent or less (except Experiment 35), the injection was so made that the drug was driven away from the area included between Dorsal I and IX (figs. 2 and 3). Contrast Experiment 8 with Experiment 9; in both, 0.1 cc. of 1 per cent novocaine and adrenalin was injected at Dorsal IV. In Experiment 8, in which the drug was driven towards the tail, the fall was 37 per cent; in Experiment 9, in which the solution was driven towards the head, the fall was 10 per cent. Again, in Experiment 16, 0.4 cc. of 2 per cent solution was injected at Cervical III caudad; the fall was 33 per cent; in Experiment 4, 0.4 cc. of 2.5 per cent solution, injected caudad from Dorsal II, much nearer the fall-producing area, was followed by a fall of 73 per cent. The conclusion again appears justified that with moderate but adequate doses, the fall in blood pressure in spinal anaesthesia is caused by paralyses in the splanchnic area.

The clinical use of spinal anaesthesia is limited to the injection of the drug in the lumbar region. As the drug diffuses towards the head, the first part of the vasomotor mechanism affected by it will be the roots in the thoracic area. It seems justifiable to assume that in clinical, as well as in experimental spinal anaesthesia, the fall of blood pressure is caused by paralysis of the splanchnic area.

Paralysis of respiration. Out of a total of 18 experiments in which no curare was used, the injection was made in the cervical or upper thoracic region ten times. In four of these ten injections, the drug was driven towards the tail from a point below the phrenic nerve and there was no paralysis of respiration. In the other six, the drug was injected towards the fifth cervical level; in four of these cases, respiration was paralyzed. In the other two cases, the dosage was very small (0.1 cc. of 1 per cent, 0.1 of 2 per cent novocaine and adrenalin.)

In closing this discussion of the regions affected by spinal anaesthesia, it is important to answer the very practical question, How often will surgical anaesthesia of the lumbar and sacral region be complicated by a serious fall in blood pressure or by an interruption of the breathing? In our experiments, there was but one case out of twenty lumbar injections in which the fall in blood pressure (to 55 mm.) might have

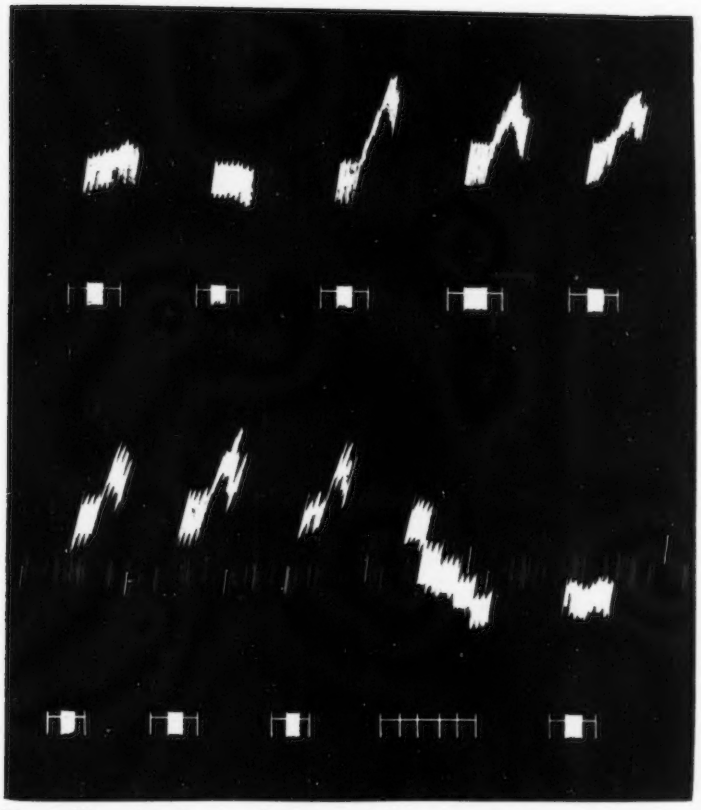

Fig. 4. The original size. Injection of 0.01 g. novocaine and adrenalin (0.2 c.c.) at Cervical II cephalad causes fall of blood pressure which is gradual rather than abrupt, due probably to slower action of drug on cord itself than on thoracic roots. Dorsal columns blocked, but vasomotor mechanism below D I is unaffected.

Lower curve—left to right		*Upper curve—left to right*	
1. Sciatic stimulation	9.40 p.m.	1. Brachial stimulation	10 05 p.m.
2. Brachial stimulation	9.43	2. Cervical II stimulation	10 07
3. Cervical II stimulation	9.46	3. Dorsal II lateral surface stimulation	10 12
4. Record of blood pressure	9.48	4. Sciatic stimulation	11 40
	(9.49 Injection of drug)	5. Brachial stimulation	11 43
	9.52		
	9.55		
	9.58		
	10.01		
5. Sciatic stimulation	10.03		

Experiment 46, curarized cat. March 4, 1915.

been serious, and in the eight injections in which no curare was used there was no paralysis of respiration.

THE STRUCTURES AFFECTED

The usual site of paralysis being in the splanchnic area, we should now enquire whether the drug affects the anterior nerve roots or the paths bringing vasoconstrictor impulses from the bulb.[5]

Since paralyses of respiration are so infrequent in spinal anaesthesia, we have not attempted to differentiate paralysis of the phrenic root fibers from that of the bulbo-phrenic respiratory path.

It may at once be stated that a strength of the drug sufficient to paralyze the afferent sensory paths (so that stimulation of the central end of the sciatic nerve produces no reflex) will also paralyze the efferent vasomotor fibers (fig. 4). This is illustrated by Experiment 23, in which 0.5 cc. of 2.5 per cent tropacocaine and adrenalin were applied to all surfaces of the cord at Cervical II. The dura at that level was laid open. The blood pressure fell from 80 to 55 mm.; stimulation of the sciatic and brachial nerves and the anterior surfaces of the cord at Cervical III produced no response. Stimulation of the anterior surface of the cord at Dorsal II, however, was followed by an excellent rise in blood pressure, thus proving the integrity of the vasomotor mechanism below the paralyzed portion.

It is possible, on the other hand, to secure paralysis of the nerve roots without disturbing the conductivity of the vasomotor paths in the substance of the cord, as in Experiment 15. In this cat, 0.2 cc. of 4 per cent novocaine and salt solution "D" was injected at Cervical III. The stimulation of the sciatic caused the blood pressure to rise from 80 mm. to 140 mm., but brachial stimulation caused no rise. The brachial roots in this experiment were paralyzed but the afferent paths conveying sciatic impulses remained unaffected.

There is some evidence to show that different functions may be affected differently. For example, Experiments 2, 3, and 8 showed that the motor paths are paralyzed more easily than the sensory paths

Experiment 2. 0.5 cc. of 1 per cent novocaine and adrenalin was injected at Dorsal XIII. Stimulation of left sciatic nerve followed by rise in blood pres-

[5] We have at present no satisfactory method of isolating effects limited to the splanchnic cells, if indeed the cells are ever paralyzed independently of the nerve paths.

sure throughout experiment, whereas right hind leg was completely paralyzed for 55 minutes.[6]

Experiment 8 shows that the vasomotor reflex may persist although spontaneous motion of the extremities is lost.

Experiment 8. In an etherized cat, 0.1 cc. of 1 per cent novocaine and adrenalin was injected at Dorsal IV at 12.04 p.m. At 12.31, 12.36 and 12.44, left sciatic stimulation was followed by rise in blood pressure from 105 to 120, 100 to 115, and 110 to 120. The right hind leg remained paralyzed for 65 minutes.

THE DIFFUSION OF THE DRUG ALONG THE CORD

In studying the diffusion of the drug along the spinal cord,[7] it seemed well to fix a reasonable interval between the moment of injection and the testing of the resultant paralysis. This period was set at fifteen minutes, in which time the drug seemed to have exerted its maximal effect. Care was taken not to manipulate the spine after the injection, lest the fluid injected should be pumped or driven to a more distant level.

Per cent of drug. In the following experiments, the same quantity of solution was injected, but the solution contained different amounts of anaesthetic (a constant mixture of novocaine and adrenalin "C"). Paralysis of the dorsal column to direct stimulation was the test employed to fix the limits to which the drug had spread.

Experiment 25. 0.225 cc. of 2.5 per cent (0.0056 g.) at Lumbar VII diffused 6 vertebrae.

Experiment 42. 0.2 cc. of 5 per cent (0.01 g.) at Lumbar VII did not diffuse 5 vertebrae

Experiment 49. 0.2 cc. of 5 per cent (0.01 g.) at Lumbar VI did not diffuse 2 vertebrae.

Experiment 50. 0.2 cc. of 10 per cent (0.02 g.) at Lumbar VII did not diffuse 4 vertebrae.

The average diffusion here was less than four vertebrae.

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[6] S. Baglioni (Centralblatt für Physiologie, 1910, xxiii, pp. 869–873), has shown that after the subdural injection of stovain, sensations disappear in this order: pain, cold, heat, pressure; they return in reverse order. This seems to show a varying degree of resistance to the effect of drugs.

[7] Some writers in this field emphasize movements of the spinal fluid due to the effects of respiration upon the emptying and filling of the cerebro-spinal venous system. That this possible factor in the diffusion of the drug is done away with when the dorsal sac is opened to atmospheric pressure, an operation found essential in our experiments, we are not prepared to deny. Other, and more important, factors affecting distribution within the dural sac can be studied by our method and indeed the problem is simplified by the removal of confusing influences.

Varying bulk of fluid. In the following experiments the amount of fluid injected was varied, while the percentage of the drug (novocaine and adrenalin "C" remained the same. The paralysis of the dorsal columns was again the test of diffusion.

Experiment 25. 0.225 cc. of 2.5 per cent (0.0056 g.) at Lumbar VII diffused 6 vertebrae.

Experiment 24. 0.25 cc. of 2.5 per cent (0.0062 g.) at Lumbar VI diffused 6 vertebrae.

Experiment 4. 0.4 cc. of 2.5 per cent (0.01 g.) at Dorsal II diffused 9 vertebrae.

Experiment 35. 0.4 cc. of 2.5 per cent (0.01 g.) at Dorsal IX diffused 11 vertebrae.

Experiment 48. 0.8 cc. of 2.5 per cent (0.02 g.) at Lumbar VII diffused 8 vertebrae

The average diffusion was eight vertebrae.

Additional information is afforded by certain experiments in which the drug was injected at approximately the same levels (Lumbar VI or VII) but in which dilute and concentrated solutions are examined with regard to their effect upon blood pressure. The greater the fall, the further the drug progressed toward the splanchnic area.

Di'ute solutions

Experiment 48. 0.8 cc. of 2.5 per cent (0.02 g.) caused blood pressure to fall 46 per cent.

Experiment 44. 1.0 cc. of 1.5 per cent (0.015 g.) caused blood pressure to fall 37 per cent.

Experiment 45. 1.0 cc. of 1.0 per cent (0.01 g.) caused blood pressure to fall 45 per cent.

Experiment 47. 0.5 cc. of 2.0 per cent (0.01 g.) caused blood pressure to fall 39.5 per cent.

The average fall was 41.9 per cent. The average dose was 0.014 g.

Concentrated solutions

Experiment 50. 0.2 cc. of 10 per cent caused blood pressure to fall 11 per cent.

Experiment 41. 0.3 cc. of 5 per cent caused blood pressure to fall 16 per cent.

Experiment 49. 0.2 cc. of 5 per cent caused blood pressure to fall 25 per cent.

Experiment 42. 0.2 cc. of 5 per cent caused blood pressure to fall 17 per cent.

Experiment 40. 0.2 cc. of 5 per cent caused blood pressure to fall 20 per cent.

The average fall was 17.8 per cent. The average dose was 0.013 g.

The analysis of the observations on diffusion does not show any very definite laws, probably because the number of experiments is

necessarily limited. On the whole, the bulk seemed a factor of greater importance than the strength of the solution. Dilute solutions seemed to spread further than concentrated solutions. But in some cases, a dose of small bulk and containing a small amount of the drug produced a more widespread effect than a dose larger both in bulk and in percentage of drug injected in a manner as nearly similar as possible.

Effect of gravity. We are aware of the possibility of error in attempting to determine the effect of gravity upon the diffusion of a drug injected into a dural sac which is exposed at the highest point to atmospheric pressure, whereas normally the cord is protected by its bony envelope. To avoid this source of confusion as far as possible, we tilted the animal and allowed the blood pressure and spinal fluid to become settled after the change of position, before injecting the drug. After the injection, the board was left tilted for fifteen minutes, then returned to level and the dorsal columns were stimulated to determine the extent of the diffusion.

The following experiments compare three animals in the horizontal position with four in which the head was tilted down at a varying angle.

Horizontal

Experiment 42. 0.2 cc. 5 per cent novocaine and adrenalin C at Lumbar VII, did not diffuse 5 vertebrae.

Experiment 49. 0.2 cc. 5 per cent novocaine and adrenalin C at Lumbar VI, did not diffuse 2 vertebrae.

Experiment 29. 0.2 cc. 5 per cent novocaine D at Lumbar VII, diffused 3 vertebrae.

Tilted, head down

Experiment 31. 0.2 cc. 5 per cent novocaine D at Lumbar VII, diffused 6 vertebrae.

Experiment 32. 0.2 cc. 5 per cent tropacocaine and adrenalin at Lumbar VII, diffused 7 vertebrae.

Experiment 39. 0.2 cc. 5 per cent novocaine D in 5 per cent glucose at Lumbar VII, diffused 8 vertebrae.

Experiment 40. 0.2 cc. 5 per cent novocaine C in 5 per cent glucose at Lumbar VII, diffused 8 vertebrae.

It appears that tilting the animal board at an angle of 40, head down, increases the diffusion of novocaine and salt solution, and that the diffusion is increased to a slight degree when the drug is carried in a 5 per cent glucose solution.

Fixation of the drug. The complete fixation of the drug in some loose chemical combination with the tissues of the cord would be greatly

to the advantage of the surgeon. If such a bond existed, the action of the anaesthetic would soon be localized. If the paralysis had extended far enough to affect seriously the blood pressure, the patient could then be tilted head down, thus keeping by the force of gravity a supply of blood in the brain. If, however, it can be demonstrated that the drug is not entirely fixed, it would follow that tilting the patient might cause the unfixed remainder of the anaesthetic to flow towards the head, invading more of the splanchnic region, and even reaching the phrenic cells, and finally the spinal bulb.

We present three observations upon fixation:

Experiment 34. One cc. of 1.0 per cent tropacocaine and salt solution was injected at Lumbar VII. Twenty minutes later, stimulation of Lumbar I produced a fair rise in blood pressure. Five minutes after that, the dura at Lumbar III was opened. Evidently the manipulation drove the drug upwards, for after that Lumbar I no longer reacted.

Experiment 38. 0.4 cc. of 5.0 per cent novocaine and salt solution D was injected at Cervical III. Blood pressure fell from 100 to 90 mm., but returned to 100 mm. in 13 minutes. Sixteen minutes after the injection, the dura was opened at Dorsal X and as the spinal fluid flowed down the cord the blood pressure fell from 100 to 80.

Experiment 40. 0.2 cc. of 5.0 per cent novocaine and adrenalin C was injected at Lumbar VII. Paralysis of the sciatic did not occur. Eighteen minutes after the injection, the board was tilted and immediately afterwards complete paralysis of the sciatic was found to have taken place.

From these three experiments we may conclude that after 25, 16, and 18 minutes respectively, enough drug free from fixation was present to paralyze other nerve fibers.

THE DURATION OF THE PHENOMENA

The duration of paralysis of the vasomotor reflexes was studied in relation to the absolute amount of drug injected, and also in relation to the percentage of the drug in solution. In many cases, a low dosage or one of weak percentage (1 to 2 per cent) secured as long a paralysis as did stronger or larger doses. The minimum dose could not be determined with any finality, for in one experiment 0.1 cc. of 1 per cent solution would be fairly effective, while in another a much larger dose would not give the desired effect.

In Experiments 26, 27, 29, and 30, the spinal fluid was drained off 15 minutes after the injection of the solution, but this did not shorten the duration of the paralysis.

In Experiments 5, 6, 8, 20, 21, 22, 24, and as the effects of the drug began to wear off, the stimulation of the sciatic nerve was followed by a fall of blood pressure instead of a rise. In cases in which this phenomenon occurred, the normal reflex returned before the blood pressure rose to its original level.

THE INFLUENCE OF ADRENALIN

In order to learn whether adrenalin was a factor in the phenomena following spinal anaesthesia, we twice injected adrenalin chloride alone.

Experiment 37. 0.5 cc. of 1–10,000 adrenalin chloride was injected cephalad from Dorsal XI. No change in blood pressure followed, but sciatic reflex was temporarily diminished, perhaps because the solution was cool.

Experiment 38. 0.5 cc. 1–10,000 adrenalin chloride, warmed, was injected caudad from Cervical III. The blood pressure fell from 120 to 110 in five minutes. The reflexes were not affected.

A comparison of the action of novocaine and adrenalin C with that of novocaine and salt solution D is given in Table 3. The injection was caudad in Experiment 15 and cephalad in all the others.

TABLE 3

Comparison of action of novocaine + salt ("D") and novocaine + adrenalin ("C")

EXPERIMENT	DOSE	LEVEL	TIME OF ONSET ON BLOOD PRESSURE	PER CENT OF BLOOD PRESSURE FALL	DURATION OF PARALYSIS		PARALYSIS DORSAL COLUMNS	PARALYSIS OF ROOTS
					of blood pressure	of reflexes		
				per cent				
15–D	0.2 cc. of 4% (caudad)	C. III	3	20	25	26	No	Yes
17–C	0.2 cc. of 4% (cephalad)	C. III	3	5	5	0	No	No
29–D	0.2 cc. of 5%	L. VII	0	0	0	25		Yes
42–C	0.2 cc. of 5%	L. VII	3	16	60+	60+	Yes	Yes
30–D	0.2 cc. of 5%	L. VII	Rise		0	27	Yes	Yes
49–C	0.2 cc. of 5%	L. VI	9	25	23	28+	Yes	Yes
36–D	0.2 cc. of 5%	C. III	Rise			35	Yes	?
46–C	0.2 cc. of 5%	C. II	12	46	110+	110	Yes	?
38–D	0.4 cc. of 2.5%	C. III	0.5	9	4	20	No	Yes
16–C	0.4 cc. of 2%	C. III	3	33	16+	0	No	Yes
39–D	0.2 cc. of 5% glucose	L. VII	0	0	0	105+	Yes	Yes
40–C	0.2 cc. of 5% glucose	L. VII	3	20	60	60	Yes	Yes

Table 3, showing six pairs of experiments, exhibits a markedly greater fall of blood pressure in the cases in which adrenalin was used. This occurs in five of the six pairs. In the remaining pair, the fall of blood pressure with novocaine and salt is not great (20 per cent). We do

not attempt to explain this fact. It may be that the pressure of salt in solution D is a factor.

It is also noteworthy that although in three experiments the novocaine D was more effective as regards duration of paralysis of the reflexes, the average duration of the paralysis after use of D was 40 minutes, whereas, of the four experiments in which C produced paralysis at all, the average duration was 64 minutes. The longest action of D was secured when the solution was made up in 5 per cent glucose. C failed twice to produce paralysis; D never failed. On the whole, the honors seem to be divided fairly evenly.

MEASURES TO RAISE THE FALLEN BLOOD PRESSURE

In five experiments an effort was made to raise the lowered blood pressure by the intravenous injection of salt solution, adrenalin chloride or pituitrin. This was done both when the blood pressure was lowered by section of the cord, and by spinal anaesthesia. To be of value, such experiments should be done only after section of the cord as otherwise the natural return of blood pressure as the spinal drug wears off will influence the results.

Saline solution, in the two experiments in which it was injected intravenously, did not materially affect the blood pressure.

The effect of pituitrin and adrenalin were tried with the cord cut across at Cervical III. Blood pressure stood at 50 in Experiment 36, at 55 in Experiment 38. In Experiment 36, 0.5 cc. pituitrin in 5 cc. H_2O was given. The blood pressure rose in one minute from 50 to 100, and four minutes later had fallen again to 60.

In Experiment 38, 0.5 cc., 1-10,000 adrenalin chloride in 5 cc. NaCl was given. The blood pressure rose from 55 to 160 at once, but in four minutes after the injection was back at 50.

CONCLUSIONS

1. In our experiments on spinal anaesthesia, there was in twenty animals but one case in which a moderate but adequate injection in the lumbar region caused a fall in blood pressure that might have been serious (to 55 mm.); and in the eight cases in which no curare was used there was no paralysis of respiration after lumbar injection.

2. Even after marked falls in blood pressure partial but sufficient recovery took place in from 30 to 90 minutes. The duration of low blood pressure appeared to depend more upon the amount of drug injected than upon the site of the injection.

3. The fall in blood pressure seen after lumbar and dorsal injection is due to paralysis in the splanchnic region. In our numerous observations, it was not due to paralysis of the bulbar vasomotor center.

4. A strength of the drug sufficient to paralyze the afferent sensory paths in the cord (so that stimulation of the central end of the sciatic nerve produces no reflex) will also paralyze the efferent vasomotor fibers.

5. The nerve roots may in some cases be paralyzed without disturbing the conductivity of the vasomotor paths in the substance of the cord.

6. There is some evidence that different functions may be affected differently; thus in three experiments the motor paths were paralyzed more easily than the sensory paths.

7. Regarding the diffusion of the drug, the bulk seemed on the whole a factor of greater importance than the strength of the solution. Dilute solutions usually but not always spread further than concentrated solutions.

8. Gravity is a factor of some importance; tilting the animal at an angle of 40°, head downward, increased the diffusion of the drug.

9. Fixation of the drug is only partial. In three experiments, after 25, 16, and 18 minutes respectively, enough remained free to paralyze other nerve fibers.

10. In seven experiments, as the effect of the drug began to wear off, the stimulation of the sciatic nerve caused a fall of blood pressure instead of the usual rise. In these cases, the normal reflex rise returned before the blood pressure attained its original level.

11. A greater fall of blood pressure occurred in the cases in which adrenalin was used in connection with tropacocaine or novocaine.

12. Measures taken to raise the fallen blood pressure were of little value. It was easy to restore the blood pressure to normal but the normal level could be maintained but a few minutes.

THE CONDUCTION WITHIN THE SPINAL CORD OF THE AFFERENT IMPULSES PRODUCING PAIN AND THE VASOMOTOR REFLEXES

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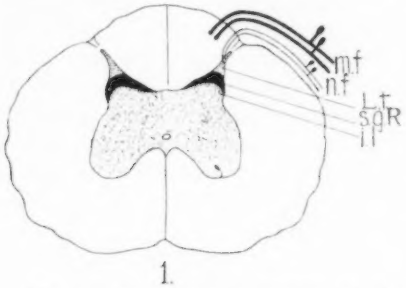
One of the problems which has been puzzling investigators for many years is that of the varieties of cutaneous sensation. How are impressions of pain, touch, heat and cold differentiated, and how are the underlying afferent impulses propagated along peripheral nerves and the spinal cord. So far as the peripheral nerves are concerned the problem has remained very obscure, and yet in the last decade advances have been made in our knowledge of the physiology and histology of afferent nerve fibers which promise to throw some light on the question.

On the physiological side Head (1) has shown that cutaneous sensations fall into two groups. In general it may be said that pain and temperature correspond to his "protopathic" group and light touch to his "epicritic." He has shown that there must be two kinds of cutaneous afferent nerve fibers corresponding to his two types of sensation. Fibers of one kind mediate protopathic sensation; fibers of the other sort mediate epicritic sensation. These two kinds of fibers differ as to anatomical distribution and rate of regeneration.

On the histological side Ranson (2) has shown that there are two kinds of afferent nerve fibers, the medullated and non-medullated. Although the non-medullated afferent nerve fibers are very numerous, in some nerves more than twice as numerous as the medullated, they remained unknown, until in 1911 a differential axon stain was developed and applied to the peripheral nerves. A remarkable parallel exists between Head's account of the protopathic fibers and the facts which have already been ascertained in regard to the non-medullated fibers. Space does not permit us to make a detailed comparison. We will restrict ourselves to a comparison of their course in the spinal cord. Head's protopathic fibers after entering the cord turn at once into the

gray matter. The epicritic fibers ascend for longer or shorter distances in the posterior funiculus before they enter the gray matter. This difference in the arrangement of the protopathic and epicritic fibers in the cord corresponds exactly to the difference in the course of the medullated and non-medullated dorsal root fibers. While most of the medullated fibers enter the posterior funiculus, all the non-medullated fibers turn at once lateral-ward into the tract of Lissauer in the apex of the posterior gray column (fig. 1.) Their course up or down the cord in Lissauer's tract is very short, the length of one or two cord segments. There is good reason to believe that they terminate in the substantia gelatinosa Rolandi (fig. 1), and that this is the nucleus of reception of these non-medullated afferent fibers.



1.

Fig. 1. Diagrammatic section of the spinal cord of the cat at the level of the first lumbar segment. *m.f.*, medullated dorsal root fibers; *n.f.*, non-medullated dorsal root fibers; *L.t.*, Lissauer's tract, *s.g.R.*, substantia gelatinosa Rolandi; *i.l.*, intermediate layer.

On the basis of many such points of similarity between the protopathic and the non-medullated afferent fibers one of us formulated the theory (Ranson 1914) that the non-medullated afferent fibers conveyed pain and temperature sensation. It was suggested that the tract of Lissauer, the substantia gelatinosa Rolandi, and the bundle of non-medullated fibers in the ventrally lying intermediate layer (fig. 1) constituted a mechanism for the reception and conduction of pain and temperature sensations. It was further suggested that this assumption "does not exclude the possibility that we are dealing here with a center for vasomotor and pilomotor control, as suggested by Sano. In fact these autonomic functions are of necessity closely correlated with the afferent impulses which find their conscious expression in the form of sensations of pain, heat and cold. It is thus possible that the apparatus in question has a double function, serving as a central autonomic apparatus and for the reception and conduction of pain and temperature sensations."

It has been pretty well established that pain is transmitted up the cord in the anterior part of the lateral funiculus (Van Gehuchten (3),

Petrén (4), Piltz (5), Bertholet (6), May (7) and Rothman (8)). Ziehen (9) however stated that pain is conducted upward in the apex of the posterior horn; and we were inclined, because of our studies on the tract of Lissauer, to believe that he was correct. At least it seemed probable that the apex of the posterior horn was an important part of the mechanism for the reception, and conduction of the "nociceptive" (Sherrington (10)) afferent impulses which are represented in consciousness by the sensation of pain.

With such possibilities in mind we determined to make a careful study of the conduction within the cord of the nociceptive afferent impulses. Such a study divides itself into two parts, dealing first, with the conduction of these impulses to the cortical centers for conscious pain, and second, with the conduction of these impulses to the centers for the autonomic reflexes, notably the vasomotor center. It will be clear that the paths in the cord for the conduction of these impulses to the cerebral cortex on the one hand and to the autonomic centers on the other need not necessarily be the same. The study of paths in the spinal cord for the nociceptive afferent impulses as determined by the ordinary tests for pain and as determined by the vasomotor reflexes forms two mutually supplementary lines of investigation which have been carried out by us on the same series of animals. The results of both lines of investigation can, therefore, be directly compared.

TECHNIQUE

Cats were used throughout this series of experiments. Various spinal cord lesions were produced, and after recovery each cat was subjected to two kinds of tests to determine the effect of the lesion, first, on the conduction of pain; and second, on the character of the vasomotor reflexes. To avoid possible variations according to age only full grown cats were used.

The operations were made at the level of the first lumbar segment, which lies under the spine of the second lumbar vertebra. A very high grade of asepsis was maintained. In addition to the usual procedures to secure asepsis, three special precautions were taken. All skin was excluded from the operative field by sterilized oiled muslin placed under the laparotomy-sheet and slit to correspond to the skin incision. The cut edges of the skin and the margins of the slit in the muslin were held together by skin clips in such a way that no skin could be seen through the opening in the laparotomy-sheet. The operator's

fingers were kept out of the wound, and gauze, needle and sutures were handled only with instruments. In closing the wound a layer of superficial fascia was drawn over the line of closure in the deep fascia and sutured to the deep fascia half an inch beyond this line. This layer of superficial fascia becomes adherent to the deep fascia in a few hours and forms a perfect protection for the deeper part of the wound. In a few cases the cutaneous incision was torn open by the cats, but in none of the twenty-five did infection develop beneath this layer of imbricated superficial fascia.

The dura was exposed and opened in the usual way. Dorsal and lateral hemisections and sections of the posterior funiculis were made with a small sharp knife. The apex of the posterior horn was destroyed on both sides of the cord in six cats by dissecting with a specially designed probe between the dorsal and lateral funiculi. All lesions were made in the first lumbar segment, except in four of the earlier experiments, in which by mistake the lesion was in the second and one in which it was in the third lumbar segment.

Attempts to produce ventral hemisections were unsuccessful. Each of the three trials resulted in serious injury to the lumbrosacral cord, probably due to a disturbance of its blood supply. From all the other operations the animals recovered promptly and moved about normally after periods varying from two days to two weeks, except in the case of cat A3 in which there was permanently some disturbance of motion and some atrophy of the hind limbs. The cats gained in weight and were in excellent condition when their vasomotor reflexes were tested.

The pain sense was tested in the unanaesthetised animals by pricking with a needle and by pinching the skin. These crude methods of inducing pain were regularly supplemented by the use of the cutaneous needle electrodes, used by Martin, Porter and Nice (11) in determining the "sensory threshold for faradic stimulation in man." Faradic stimulation of uniform strength through these electrodes gives much more uniform and dependable pain reactions than can be obtained by pinching or pricking the skin. The cord lesion was at the level of the first or second lumbar segments and hence above the level of origin of all the nerves going to the hind limb. All tests of the hind limbs were made over the area of distribution of the sciatic nerve which takes origin below the level of the fifth lumbar segment. A sharp cry and generalized struggling movements were taken as criteria of pain.

After complete recovery of the animal from the lesion and after the conduction of pain in the cord had been tested the vasomotor reflexes were studied. Under ether anaesthesia a tracheotomy was performed and the ether bottle attached. Connections were made as rapidly as possible for carotid blood pressure and respiratory tracings. Both sciatic nerves were exposed, ligated and cut distally to the ligature. The central end was laid bare for some distance above the ligature and could be handled by the attached thread. On the left side three brachial nerves, the median, ulnar and internal cutaneous were exposed, ligated together, and cut distally to the ligature and thereafter treated as a single nerve. Care was taken not to stretch the nerves at any time. When not being stimulated, they were kept covered with other tissues to prevent drying.

To eliminate passive dilatation of blood vessels in the areas supplied by the divided nerves the limbs were constricted with heavy cord placed proximal to the elbow and knee joints. Fluctuations in blood pressure from pressure on the abdomen by flexion of the limbs during stimulation of a nerve were prevented by securely tying the legs to the animal board.

The stage of ether anaesthesia is of the greatest importance as the vasomotor reflexes are affected by the slightest overdose, (Porter (12)). This seems to be especially true of the depressor reflex which is difficult to obtain under deep anaesthesia. The animal was kept relaxed, with regular respiration, with pupils half contracted, and with a brisk corneal reflex. Any tendency toward cyanosis was prevented because asphyxia, being a powerful vaso-constrictor stimulus, would obscure the results of sciatic stimulation (Sollman and Pilcher (13)).

Faradic stimulation of the central ends of the cut nerves was used to elicit the reflexes. Standard platinum electrodes were applied at least half an inch from the cut ends of the nerves, held suspended by the threads with which they had been ligated. The electrodes were moved slowly along the nerve during stimulation. The source of the current was a Stoelting inductorium No. 7090 through the primary of which passed a constant half ampere current. The primary current was obtained by shunting the instrument circuit across part of the resistance of a two ampere one hundred ten volt direct current "individual unit" system (von Hess (14)) attached to an ordinary lamp socket. By actual observation at repeated intervals the current through the primary coil was found to be very constant. The rate of interruption of the primary current was made fairly slow, about 25 per

second, in order to avoid possible overlapping of the currents induced in the secondary coil (Erlanger 1914). A knife switch in the primary circuit insures uniform contact. It is believed that with this system the strength of the induced current for each position of the secondary coil does not vary greatly from day to day. In this way stimulation of the same strength can be applied to several nerves in the same cat and to the nerves of different cats and the results compared.

Curare was used in some of the experiments. It was injected intravenously very slowly, until the stimulation of the peripheral end of a cut nerve gave no response.

After the reflex vasomotor and respiratory responses had been recorded the animal was killed, the cord exposed and the level of the lesion accurately determined. A stretch of cord about seven millimeters long containing the lesion was removed and prepared by the pyridine-silver method (Ranson (2)) and cut into serial sections. The serial sections were then studied to determine the extent of the lesion.

LITERATURE ON THE VASOMOTOR REFLEXES

There is a vast number of articles on the conduction of pain in the spinal cord. Good reviews of this literature have been given by Bertholet (6), May (7) and Karplus and Kreidl (15).

Considerable work has been done on the vasomotor reflexes, but relatively little is known concerning the anatomical location of the reflex arcs involved. It is generally stated that there exists in the brain stem a center for the regulation of blood pressure. It is supposed that this is primarily a vasoconstrictor center and is associated with the pressor reflexes. Little or nothing is known concerning the location of a center or centers for the depressor reflexes. In addition to the "principal" vasomotor center in the bulb "secondary" segmental centers are located in the thoracic and upper lumbar portions of the spinal cord, i.e., in those segments of the cord with which the white rami are associated.

Concerning the paths in the cord along which afferent impulses ascend to the vasomotor centers little is known. Dittmar (16) obtained the usual pressor effects from sciatic stimulation after section of the posterior columns and gray matter of the spinal cord. Sherrington (17) obtained results which led him to conclude that the afferent path to the vasomotor center lay in the anterior part of the lateral funiculus and states that Miescher had previously obtained similar

results. Bikeles (18) also reports some experiments which led him to the same conclusion. None of these papers give evidence of a thoroughgoing investigation of the question and the results are open to numerous objections such as the testing of the vasomotor reflexes before the animal has recovered from the effects of the operation, the location of the lesion too high (9th Th. Seg.) and the failure to distinguish between pressor and depressor reflexes.

Aside from these experiments little has been done to determine the effects of cord lesions on the vasomotor reflexes. Stursberg (19) showed that complete destruction of the cord at the level of the 7th thoracic segment involved the fibers which produced a coördination of the vasoconstrictors of the arm and leg.

The observations of Sherrington (10), Pike (20) and Porter and Muhlberg ('21) on "spinal shock" have an important bearing on our work. After transection of the spinal cord at the 8th cervical segment or during complete cerebral anaemia the blood pressure falls but soon returns to normal. The vasomotor reflexes are at first abolished but return in a short time. According to Sherrington the pressor reflex becomes very good after a few weeks and must now be purely spinal.

It has recently been shown that stimulation of the central end of the sciatic produces depressor or pressor reflexes according to the strength of the stimulus. (Porter (12), Sollman and Pilcher (22), Martin and Lacey (22).) Weak stimulation gives depressor reflexes, strong stimulation gives pressor reflexes. Martin and Lacey argue that the depressor reaction from sciatic stimulation is the more normal, since the pressor reactions are produced only by excessive stimulation.

VASOMOTOR REACTIONS IN NORMAL CATS

In order to determine the character of the normal vasomotor reactions we obtained tracings from fourteen normal adult cats. In all of these, excepting two, stimulation of the sciatic or brachial nerves with strong currents (s.c. 4 to 6 = secondary coil at 4 to 6) gave an increase in blood pressure, Table I. This pressor response varied considerably in extent. The cat giving the least response showed a rise in blood pressure of 11 mm. The greatest reaction obtained from these normal cats was a rise of 48 mm.

Stimuli in the depressor range (s.c. 13 to 18) were given to nine of these normal cats. They all showed a drop in blood pressure varying in extent from 4 to 22 mm. Hg. With medium strengths of current the results varied greatly, some cats showing a rise others a fall in blood pressure. These results corroborate those of Porter (12), Sollman and Pilcher (22) and Martin and Lacey (23) that stimulation of the central ends of afferent spinal nerves gives depressor reflexes with weak and pressor reflexes with strong stimulation. In the theoretical discussion of our results we will attempt to give an explanation of

TABLE I.

Normal cats.

CAT	INITIAL BLOOD PRESSURE	CHANGES* IN BLOOD PRESSURE IN MM. HG. FOR INDICATED POSITIONS OF SECONDARY COIL							
		17-18	15-16	13-14	11-12	9-10	7-8	5-6	4-5
N. 4	142								+13
N. 5	129								+ 9
N. 6	139								+23
N. 7	140								+11
N. 8	121				+18	+14			+48
Ex. 1	122	− 8	−11	− 5	−22	−14	−12	−11	
Ex. 2	144	−15			+45			+38	
Ex. 3	130	− 9	−12	−18	−18	−14	−11	+24	+10
Ex. 4	154	−22			−28	−26		+24	+24
Ex. 5	124	− 6	− 4		−10			+14	+ 8
Ex. 6	171	− 8			−18	−22		−16	
Ex. 7	144	−22				−20		+24	+16
Ex. 8	153	− 3	− 6					+20	
Ex. 9	178	−10	−20					+38	

*A rise in blood pressure is indicated by +, a fall by −.

this change in direction of the reflexes with increasing strengths of stimulation.

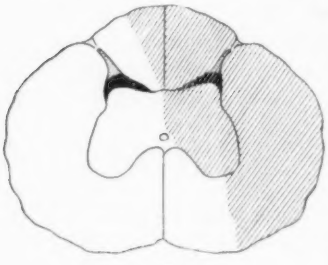
In our series of normal cats the sciatic nerve was used almost exclusively. Occasionally, however, tests were made on the brachial nerves—median, ulnar and internal cutaneous being stimulated alone or together. So far as our results show there was no difference in the reflexes obtained from sciatic and brachial nerves. This agrees with the observations of Porter and Richardson (24), who found by a long series of experiments with stimuli of given intensity, applied to the sciatic and brachial nerves in cats and other animals, that the result did not depend in any

way on which afferent spinal nerve was stimulated. These experiments were all with strong stimuli in the pressor range. Weak stimulation also gives a depressor response which is independent of the individual nerve stimulated, (Martin and Lacey (23)).

LATERAL HEMISECTIONS

The vasomotor reflexes were tested on five cats which had suffered a right lateral hemisection of the spinal cord 17 to 63 days before the tracings were taken. All five had recovered perfectly and had full use of both hind legs.

Post mortem examination showed the lesion located in the first lumbar segment in three of these cats and in the second lumbar segment in two. In one (cat O 7) the lesion when studied microscopically proved to be a perfect hemisection. In all the others part or all of the right anterior funiculus escaped injury (fig. 2). In two the lesion extended slightly beyond the mid line posteriorly into the left posterior funiculus (fig. 2). Since the conduction of pain and the reflex changes in blood pressure were the same in cat O 7 in which the hemisection was a perfect one as in the others in which the lesion was incomplete ventrally we conclude that these variations in the lesion have not affected the results.



2.

Fig. 2. Diagram of the second lumbar segment of cat O 8. The shaded area shows the part involved in the right lateral hemisection.

As far as could be determined by pricking the skin and by the use of cutaneous needle electrodes pain was conducted up the cord equally well from all four legs. We had hoped that by the use of the cutaneous electrodes we could locate accurately the pain threshold and determine if there were any difference on the two sides of the body below the lesion. We found that the threshold on the normal limb varied considerably and these normal variations were greater than any difference between the two hind limbs or between the front and the hind limbs in cats with lateral hemisection of the cord. We do not deny that in the cat some difference may exist in the conduction of pain from the two sides after lateral hemisection but such difference as may exist is too small to be readily recognized. In the same way we found it impossible

TABLE II

Depressor reflexes after lateral hemisection

CAT	POSITION OF SECONDARY COIL	NERVE	DROP IN BLOOD PRESSURE IN MM. HG. Individual tests	AVERAGE
0–6 I. B. P. 166	16	Brachial	22 18	20
		Right sciatic	24 22	23
		Left sciatic	5 5 8 5	6
	14	Brachial	20 19 31 27	24
		Right sciatic	21 19 25 26	23
		Left sciatic	5 5 14 11	9
0–7 I. B. P. 166	16	Brachial	21 19	20
		Right sciatic	21 20	21
		Left sciatic	−4 −5 0 5	−1
	14	Brachial	20 18 31 28	24
		Right sciatic	21 18 27 26	23
		Left sciatic	3 3 13 9	7
0–8 I. B. P. 142	12	Brachial	20 19 13	17
		Right sciatic	19 18 7	15
		Left sciatic	9 −3 9 9	6
	8	Brachial	16	16
		Right sciatic	23	23
		Left sciatic	5	5
A–4 I. B. P. 166	18	Brachial	15 15 16	15
		Right sciatic	18 13 11 0	11
		Left sciatic	7 8 9	8
	16	Brachial	14 23 22	20
		Right sciatic	20 10 12 8	13
		Left sciatic	16 13 9 5	11
A–5 I. B. P. 176	17	Brachial	12	12
		Right sciatic	15	15
		Left sciatic	5	5

to demonstrate any loss in sensibility to pain in the hind limbs as compared to the front limbs.

It is clear that the conduction of pain in the cat's cord takes place bilaterally. This agrees with the results of other observers on animals (Bertholet (6) and May (7)). But it is usually stated that, while

TABLE III

Pressor reflexes after lateral hemisection

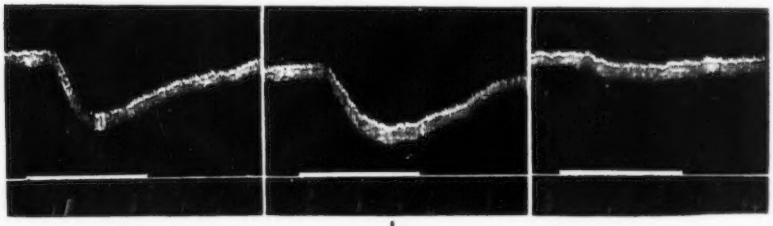
CAT	POSITION OF SECONDARY COIL	NERVE	RISE IN BLOOD PRESSURE IN MM. HG.			AVERAGE
			Individual tests			
0–6 I. B. P. 123	5	Brachial	5	0	0	2
		Right sciatic	0	0		0
		Left sciatic	6	6	14	9
0–7 I. B. P. 166	5	Brachial	29×	32×		31×
		Right sciatic	0	0	0	0
		Left sciatic	9×	10×	16×	12×
0–8 I. B. P. 142	4	Brachial	12			12
		Right sciatic	0			0
		Left sciatic	8			8
	2	Brachial	15×	0	16	10
		Right sciatic	0			0
		Left sciatic	10			10
A–4 I. B. P. 158	6	Brachial	28×	25×		27×
		Right sciatic	8×			8×
		Left sciatic	11			11
	4	Brachial	26×	32×		29×
		Right sciatic	5	0	−2	1
		Left sciatic	4	0	0	1
A–5 I. B. P. 176	5	Brachial	22×	31×		27×
		Right sciatic	0			0
		Left sciatic	9	9×	9	9

× indicates that the rise was followed by a considerable fall in blood pressure.

conduction of pain is bilateral in animals, it is more contralateral than homolateral. It is usually said that after a hemisection in animals there is partial analgesia of both hind limbs and that this is most noticeable on the side opposite the lesion. Karplus and Kreidl (15) have recently shown that after section of both halves of the cord in the cat at different levels, pain is still felt in the hind limbs. This would indicate that in the cat short spinal paths take an especially important part in pain conduction. We were unable to demonstrate any hypalgesia in the hind limbs of our cats with laterally hemisected cords. Despite these negative results as to the conduction of pain, these cats

showed characteristic departures from normal in their vasomotor reactions.

As will be seen by a study of Table II the depressor reactions obtained from the brachial and right sciatic nerves were normal and approximately equal. They were of the same average extent as the drops obtained in normal cats and showed no greater variation than these. In striking contrast is the reaction obtained from the left sciatic which was as a rule not more than a third as great as that obtained from the brachial and right sciatic nerves (fig. 3.). Each nerve was stimulated several times and the results of the individual tests were very consistent as



3.

Fig. 3. Blood pressure tracings from cat O 8, with right lateral hemisection of the cord. Base line raised 57 mm. *a*, drop of 18 mm. Hg. on stimulation of the left brachial nerves with weak faradic current *s.c. 14.; b*, drop of 19 mm. Hg. on stimulation of the right sciatic nerve with weak faradic current *s.c. 14*. *c*, negligible drop on stimulating the left sciatic nerve with weak faradic current *s.c. 14*.

will be seen by the table. Each of the five cats gave the same results. It is, therefore, clear that after right lateral hemisection of the cat's spinal cord at the level of the first lumbar segment the depressor reactions obtained from the brachial and right sciatic nerves are normal while those obtained from the left sciatic nerve are greatly reduced. This would indicate that the conduction in the spinal cord of the afferent impulses producing the depressor reflexes is chiefly contralateral but to some extent also homolateral.

The changes in the pressor reflexes were not so clear. In every case the pressor reaction obtained from strong sciatic stimulation, is below the average pressor response obtained by stimulating the sciatic in normal cats with the same strength of current, Table III. With one

exception the pressor response from either sciatic was considerably less than from the brachial. Since the pressor reflexes from both sciatic nerves are decreased after lateral hemisection it would seem that the afferent impulses bringing about this rise in blood pressure must pass up the cord bilaterally.

It will be noted further that the rise from right sciatic stimulation is less than that from stimulation of the left sciatic. This may be due to the impulses passing up the cord somewhat better homolaterally than contralaterally. Or it may be due to the fact that the antagonistic depressor reflex is almost eliminated from the left side, while on the right side the depressor reflex is normal and tends to overpower the weakened pressor. It seems probable, therefore, that the afferent impulses producing a rise in blood pressure are conducted bilaterally in the cord, and either equally well on both sides or somewhat better homolaterally.

Since the best depressor reactions were obtained from the sciatic on the side of the lesion and the best pressor reactions from the sciatic on the side opposite the lesion, it is clear that the afferent paths in the cord involved in these two reflexes are not the same.

POSTERIOR HEMISECTION

A posterior hemisection was performed on six cats at the level of the first or second lumbar segments. The autopsy, performed 6 to 84 days later, showed that in two (A 1 and A 2) the lesion was in the first, in three (O 2, O 3 and A 3) in the second, and in one (O 4) in the third lumbar segment. Microscopical examinations showed that in each case the lesion involved all of the posterior funiculus, the posterior part of the lateral funiculus and all of the gray matter except the anterior horns (fig. 4). In cat O 2 the entire gray substance was destroyed at the level of the lesion.

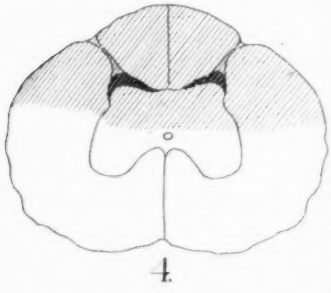


Fig. 4. Diagram of the second lumbar segment of cat A 3. The shaded area shows the part involved in the posterior hemisection.

So far as could be determined by careful tests these cats felt pain equally well in all four extremities. These lesions in the posterior half of the cord had had no appreciable effect on the conduction of

pain impulses from the hind limbs to the cortex. This is in keeping with the results of most other recorded experiments which place the pain path in the anterior part of the lateral funiculus. The interest in these experiments lies in the fact that they show, contrary to the assumption on which this investigation was started, that the apex of the posterior horn is at least not the chiefh of pat pain toward the cerebral cortex. It is also of interest to note that in cat O 2 the gray matter was completely destroyed at the level of the lesion, showing that pain is not transmitted upward in the gray matter of the cord.

The vasomotor reactions on these cats were tested from 6 to 84 days after the operation. It was found that in each animal stimulation

TABLE IV

Reflex changes in blood pressure after posterior hemisection

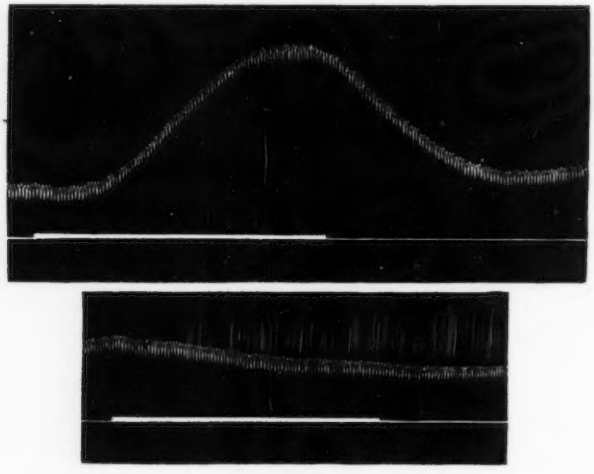
CAT	INITIAL BLOOD PRESSURE	POSITION OF SECONDARY COIL	CHANGES IN BLOOD PRESSURE IN MM. HG.		
			Brachial	Right sciatic	Left sciatic
O–2	138	4.5	$+18^{2}$	-2^{5}	-2^{5}
O–3	152	4.5	$+31^{2}$	$+3^{2}$	$+3^{2}$
O–4	148	4.5	+29	+15	+15
A–1	148	6.0	$+21^{2}$	-1^{2}	-13^{2}
A–2	160	8.0	$+16^{2}$	0^{2}	$+4^{4}$
A–2	160	0.0	+20	−3	−2
A–3	104	6.0	+14	−8	−6
A–3	104	4.0	+12	−8	−8

+ indicates a rise.
− indicates a fall.
Small figures indicate the number of individual tests which have been averaged.

of the brachial nerves with strong currents (s.c. 0 to 8) gave normal pressor responses varying in height from 12 to 31 mm. Hg. (Table IV). With the same stimulation little or no response was obtained from either sciatic (fig. 5). The slight reaction obtained was more often a drop than a rise. In one cat a rise of 15 mm. Hg. was obtained from sciatic stimulation, but in this animal we had failed to tie the legs securely to the animal board and it is possible that flexion of the thigh on the abdomen may have caused this rise by increasing intra-abdominal pressure. Leaving this result to be explained, the other five cats showed a negligible rise of 3 to 4 mm. Hg. or a drop of 2 to 8 mm. Hg. on sciatic stimulation with currents that gave strong pressor reactions from the brachial nerves. It is thus clear that the nociceptive impulses which

produce a reflex rise in blood pressure travel up the posterior half of the spinal cord along paths which are not the same as those taken by the nociceptive impulses toward the cortical centers for conscious pain.

No systematic attempt was made in these cats to develop the depressor reflex with weak stimulation. Such tests, as were made, indicate that the depressor mechanism was either normal or somewhat



5.

Fig. 5. Blood pressure tracings from cat O 3 with posterior hemisection of the cord. Base line raised 57 mm. Upper tracing, rise of 42 mm. Hg. on stimulation of the left ulnar with strong faradic current *s.c.* 4½. Lower tracing, slight drop on stimulation of the right sciatic with strong faradic current *s.c.* 4½.

reduced in activity. No exaggerated depressor reactions were obtained in this series.

This question now suggests itself: What part of the posterior half of the cord is involved in this pressor vasomotor reflex? The following paragraphs will show that it is not the posterior funiculus.

SECTION OF THE POSTERIOR FUNICULUS

At the level of the second lumbar segment the medial three-fourths of the posterior funiculus contains all of the dorsal root fibers of the lower lumbar and sacral roots which have reached this height in the

cord. The lateral one-fourth at this level contains only fibers from the second and third lumbar nerves. Hence by cutting the medial three-fourths of the posterior funiculus in the second lumbar segment, as was done in cat O 9, it is possible to cut all the fibers in this funiculus associated with the sciatic nerve and yet run no risk of injuring the apex of the posterior horn. This was attempted in two cats. In cat O 10, the apex of the posterior horn was damaged on one side and the vasomotor reactions showed evidences of this. But in cat O 9 a satisfactory lesion was obtained, although in this cat in addition to a section of the medial three-fourths of the posterior funiculus considerable damage was done to the gray matter around the central canal (fig. 6).

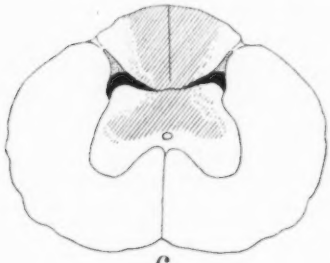


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Fig. 6. Diagram of the second lumbar segment of cat O 9. Shaded area shows the part involved in the section of the medial three-fourths of the posterior funiculus.

As was to be expected from the results on posterior hemisection both of these cats showed no hypalgesia in either hind limb. The vasomotor reactions in cat O 9 were entirely normal (Table V). Since in this cat the impulses producing both the pressor and the depressor reactions traveled up the cord in a normal manner it is clear that the posterior funiculus takes no part in the conduction of the nociceptive impulses to the vasomotor centers.

TABLE V

Reflex changes in blood pressure after section of the posterior funiculus—Cat O 9

INITIAL BLOOD PRESSURE	POSITION OF SECONDARY COIL	REFLEX CHANGE IN BLOOD PRESSURE IN MM. HG.		
		Brachial	Right sciatic	Left sciatic
142.....	16	−14	−10	−27
	6	+31	+28	+20

− indicates a fall.
+ indicates a rise.

BILATERAL LESIONS IN THE APICES OF THE POSTERIOR HORNS

In the apex of the posterior horn is situated the tract of Lissauer and the substantia gelatinosa Rolandi. These structures are associated with the dorsal roots and belong on the afferent side of the nervous system. But their special function has remained unknown.

Six cats were operated on with the idea of destroying the apex of the posterior horn on both sides at the level of the first lumbar vertebra. The autopsies showed the lesion in each case located in this segment, but microscopical examination showed that the lesion was fairly complete in only two cats A 6 and A 8 (fig. 7). In each of the other cats the destruction of the apex of the posterior horn was incomplete on one or both sides. In cat A 11 the tract of Lissauer was destroyed on both sides and a little of the substantia gelatinosa on one side. In cats A 7, A 10, and A 12 the tract of Lissauer was entirely destroyed on one side and more or less intact on the other. In these three cats the substantia gelatinosa suffered but little injury on either side. In cats A 6, A 8, and A 11 the bilateral destruction of the apex of the posterior horn was most complete and they gave the most characteristic vasomotor reactions.

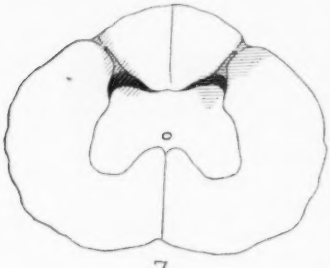


Fig. 7. Diagram of the first lumbar segment of the cord of cat A 8. Shaded area shows the part involved in the bilateral lesions of the apices of the posterior horns.

As was to be expected from the results of posterior hemisection none of these six cats showed any hypalgesia of the hind limbs. These animals tested from 11 to 23 days after the operation showed a very remarkable variation from the normal vasomotor reaction, Table VI. With weak stimulation (s.c. 16 or 17) normal depressor reactions were obtained from both sciatics and the brachial nerves. With increasing strengths of current the reflex drop became greater and greater. With normal cats the greatest drop was obtained with weak or moderate stimulation (s.c. 17 to 12) and as the current was increased beyond this optimum depressor stimulus the drop became smaller and soon gave place to a rise. The greatest drop obtained from a normal cat was 28 mm. Hg. In these cats with lesions in the apices of the posterior horn the drop continued to increase as the strength of the stimulus was

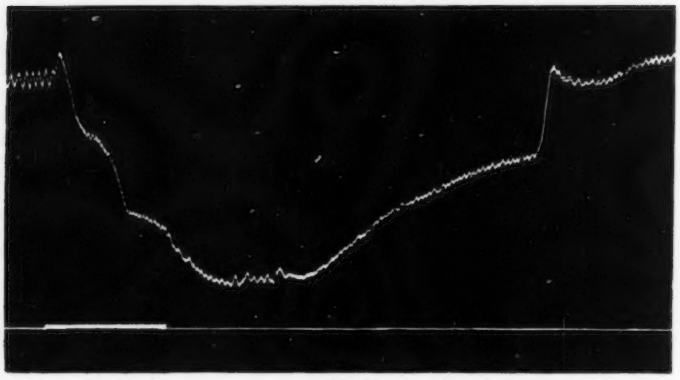
TABLE VI

Reflex changes in blood pressure after bilateral lesions in the apices of the posterior horns

CAT	INITIAL BLOOD PRESSURE	POSITION OF SECONDARY COIL	CHANGES IN BLOOD PRESSURE IN MM. HG.		
			Brachial	Right sciatic	Left sciatic
A–6	158	17	− 5	−11	− 4
		12	−12	−23	−10
		8	−46	−47	−35
		4	−29	−40	−26
A–7	136	16	− 9	− 8	0
		*4	+12	+10	+11
			−44	−32	−30
A–8	140	17	−11	−13	−12
		4	−44	−52	−42
A–10	136	17	−20	− 6	−10
		9	−21	−26	−15
		8	− 4	−11	
		*6	+28	+16	+25
			−38	−38	−31
A–11	138	17	−15	−18	−14
		12	−20	−43	−35
		9	−33	−44	−31
		6	−60	−58	−36
A–12	130	17	−10	−22	− 4
		9	−20	−28	−27
		8	−11	−27	−21
		6	+43	+28	+26

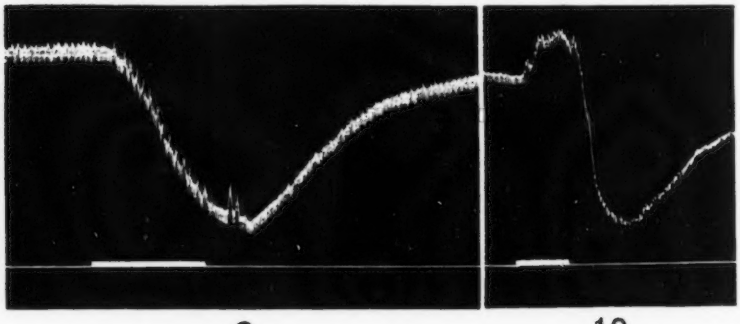
\+ indicates a rise.
− indicates a fall.
* A–7 and A–10 show rise followed by marked drop.

increased until with strong stimuli (s.c. 4 to 9) which would normally produce strong pressor responses the fall in blood pressure became two or three times as great as any that was obtained from normal cats (figs. 8, 9, 10). From the right sciatic a drop of 40 mm. Hg. was obtained with cat A 6, a drop of 52 mm. Hg. with cat A 8, and one of 58 mm. Hg. with cat A 11. It should be noted that these reactions are two or three times as great as can be obtained by stimulating the same nerves in normal cats and were obtained by strength of stimulation



8.

Fig. 8. Blood pressure tracing from cat A 11, with bilateral lesions in the apices of the posterior horns. Base line raised 26 mm. Drop of 58 mm. Hg. on stimulation of the right sciatic with strong faradic current *s.c. 6*.



9 10.

Fig. 9. Blood pressure tracing from cat A 8 with bilateral lesions in the apices of the posterior horns. Base line raised 33 mm. Drop of 52 mm. Hg. on stimulation of the right sciatic nerve with strong faradic current *s.c. 4*.

Fig. 10. Blood pressure tracing from cat A 7 with bilateral lesions, in the apices of the posterior horns. Base line raised 42 mm. Slight rise followed by drop of 44 mm. Hg. on stimulation of the left brachial nerves with strong faradic current *s.c.4*.

which would normally produce the greatest pressor reaction. No pressor responses could be obtained from these three cats. It will be noted that in all these cats the brachial nerves gave the same response as the sciatics. This is difficult to explain but an attempt at an explanation will be made later.

The cats in which the tract of Lissauer was not completely destroyed on both sides (A 7, A 10, A 12) do not give clear cut results (Table VI); but each shows a tendency for the depressor reaction to predominate. In cats A 7 and A 10 strong stimulation (s.c. 4 to 6) gave a moderate rise in blood pressure followed by a much greater fall. The character of such a reaction is shown in figure 10. The drop carried the blood pressure two or three times as far below the original level as the rise carried it above that level.

The abruptness of the drop in cats A 7, A 10, and A 11 may indicate that vagus inhibition of the heart plays an important part in this reaction. Yet this cannot be the chief cause of the fall in blood pressure since in cats A 6 and A 8 section of both vagi did not affect the reaction. In fact the tracing from cat A 8 (fig. 9) was taken after both vagi had been divided.

In cat A 12 the lesions in the tracts of Lissauer were not complete bilaterally. Well marked pressor responses were obtained from sciatic stimulation but a greater one was obtained from the brachial. The results would be easily explained on the assumption that the pressor impulses pass up in the tract of Lissauer and that the partial lesions of these tracts in cat A 12 had partially shut off these impulses arising in the sciatics from reaching the vasomotor centers. In fact the results from cat A 12, though unlike those from the other five of the series are more easily explained than the others.

The question arises, why were not pressor responses obtained from the brachial nerves in the other cats of this series? Since the brachial nerves are connected with the cord above the level of the lesion and the lesion was below the segments from which most if not all of the vasomotor fibers leave the cord, it is difficult to understand why the vasomotor responses from the brachial nerves should have been altered at all. One possible explanation would be that the cutting off of the impulses normally ascending in the apex of the posterior horn from all of the nerves below the first lumbar so lowered the tone of the series of short relays by which the impulses are transmitted that the pathway may become less conductive than normal even to impulses from the brachial nerves. But this explanation is not altogether

satisfactory and the most we can say at present is that lesions of the apices of the posterior horns in upper lumbar segments of the cord cause a complete reversal of the vasomotor responses from strong stimulation of the spinal nerves. Other experiments along this line are in progress.

EFFECT OF CORD LESIONS ON REFLEX CHANGES IN RESPIRATION

In the six cats with bilateral lesions of the apices of the posterior horns, stimulation of the sciatic caused the same increase in rate and depth of respiration as in normal cats. Since the pressor responses were eliminated in five of these cats it would seem that the afferent paths to the respiratory centers are not the same as those to the pressor vasomotor centers. Section of the medial three-fourths of the posterior funiculus also had no effect on reflex changes in respiration. We conclude that the path to the respiratory center is neither in the posterior funiculus nor in the apex of the posterior horn.

In the six cases of posterior hemisection the reflex changes in respiration from sciatic stimulation were greatly reduced though not entirely eliminated. This indicates that the impulses leading to reflex changes in respiration pass up in part at least in the posterior half of the lateral funiculus.

RELATION OF PAIN TO THE VASOMOTOR REFLEXES

All of the cats whose vasomotor reflexes were tested felt pain equally well in all four extremities. So far as could be determined none of them showed any hypalgesia. The complete elimination of the pressor reflex in many of these cats shows that within the cord the pressor path and the path for conscious pain are not the same. On the other hand the depressor reflex was not eliminated in any of these cats. This path was shown to be chiefly crossed and is probably located in the lateral funiculus. Although we could not demonstrate that the pain path was chiefly crossed in cats this has been shown to be the case in most other mammals and in man. It may be that the more accurate blood pressure tracings showed a difference in the two sides which the more crude pain tests failed to show. It is therefore possible that the afferent impulses which are felt as pain and those which produce the depressor vasomotor reactions travel the same paths in the spinal cord.

THEORETICAL CONSIDERATIONS

1. Vasomotor reflex arcs. It is difficult at first to see how the alterations in the vasomotor reflexes which we have described can be accounted for. It is possible however to formulate a conception of the vasomotor reflexes which would explain all our observations. This we present in a purely tentative way as a working hypothesis.

It has been shown by Pike (20) and Sherrington (10) that after section of the cervical cord and during cerebral anaemia the vascular tone and pressor reflexes, which are at first lost, quickly return. This in our mind throws considerable doubt on the importance of the "chief" vasoconstrictor or pressor center in the medulla and in our theory we ignore the brain entirely, although nothing in our theory would be inconsistent with the afferent paths passing by way of the medulla. It is well known that the vasomotor impulses ultimately leave the cord by way of the thoracic and upper lumbar spinal nerves. We shall consider the paths by which impulses from the sciatic ascend to the vasomotor centers without committing ourselves as to the location of these centers.

We assume that in the vasomotor reflexes there are two separate paths from the sciatic nerve to the efferent vasomotor neurones; and for brevity we will speak of a pressor path and a depressor path according to the vascular responses produced by the impulses which they carry. That these are separate paths seems to be true, since after lesions of the spinal cord one type of reflex may be decreased or destroyed while the other is normal or augmented.

The pressor path, according to this hypothesis, is in the apex of the posterior horn and is either equally bilateral or chiefly homolateral. This would account for the loss of the pressor reflex from sciatic stimulation after posterior hemisection and after bilateral injury to the apices of the posterior horns.

The depressor path is not involved in section of the posterior funiculus nor in bilateral injury to the apices of the posterior horn. It must therefore be ventrolateral to these structures probably in the lateral funiculus. Some damage seems to have been done in this path to posterior hemisection but as to this our results are not clear. The results obtained on cats with lateral hemisections showed that the depressor path was chiefly crossed.

The impulses traveling along the two paths are mutually antagonistic and in normal animals vasomotor reactions represent a balance between

them. The depressor path has a low threshold; and by it weak stimuli are able to reach the efferent vasomotor neurones. The pressor path has a high threshold since it is composed of the short fibers and many synapses of the apex of the posterior horn. With weak stimuli the impulses pass up the depressor path only, resulting in a drop in blood pressure. With stimuli of medium intensity they pass up both paths; stimulation and inhibition balance each other with little or no change in blood pressure. With strong stimuli they still pass up both paths but the strong pressor overcomes the depressor impulses, resulting in vasoconstriction and increased blood pressure.

After bilateral lesion of the apices of the posterior horn the pressor path is so impaired that with strong stimulation the inhibitory impulses along the depressor path predominate and produce marked depression. This would account for the marked depression obtained in this series from sciatic stimulation. But similar depressions were obtained from the brachial nerves in this set of experiments, although no cord lesion was interposed between the origin of these nerves and the vasomotor efferent neurones in the thoracic cord. In order to explain this result it is necessary to assume that the normally high resistance of the pressor path has been increased above the lesion by the cutting off of the impulses normally ascending in this path from the lower half of the body.

2. The intraspinal conduction of nociceptive afferent impulses. It is generally admitted that painful afferent impulses are associated with uncontrollable nervous discharge through the autonomic system, one expression of which is the vasomotor reflex (Sherrington in Schaffer's *Text of Physiology*). Obviously only such part of these impulses as ascend to the cortex are responsible for the production of pain. Hence "nociceptive" is a better general term than "painful" and includes the afferent impulses producing the pain reflexes as well as those producing conscious pain. The apex of the posterior horn is involved in the conduction of the nociceptive impulses producing reflex vasoconstriction but not in the upward conduction of those which are felt as pain. It seems probable to us that the tract of Lissauer and the substantia gelatinosa which are well developed in all vertebrates form the primitive mechanism for the reception and intersegmental conduction of nociceptive afferent impulses. In lower vertebrates there is no spinothalamic path for the conduction of painful afferent impulses toward the cerebrum, but these lower forms must have some mechanism for the reception and intersegmental conduction of nociceptive impulses. The tract of Lissauer and the substantia gelatinosa are present

in well developed form in these lower vertebrates and their structure is such that they are especially adapted for intersegmental conduction. Even in the mammal they retain the function of conduction of some nociceptive impulses as is evidenced by their relation to the pressor reflex. With the development of the cerebral cortex in the higher vertebrates this mechanism in the apex of the posterior horn would still retain, according to this theory, its function of reception of all nociceptive impulses. Connected with it there would be developed a new pathway to the cerebral cortex, the spinothalamic, which would carry the pain impulses from the primitive nociceptive mechanism to the cortical centers for conscious pain.

CONCLUSIONS

1. Lateral hemisection in the upper part of the lumbar cord results in a great reduction of the depressor reaction obtained from stimulation of the sciatic on the side opposite the lesion. The depressor reactions from the sciatic on the side of the lesion and from the brachial nerves are normal. There is considerable reduction in the pressor reactions from both sciatics, the greater reduction being in the pressor reactions from the sciatic on the side of the lesion.

2. Posterior hemisection in the upper part of the lumbar cord almost entirely obliterates the pressor reflex from sciatic stimulation but has less effect on the depressor reflex.

3. Section of the posterior funiculus in the lumbar region is without influence on the vasomotor reflexes.

4. Bilateral lesions in the apices of the posterior horns obliterates the pressor reflex. The depressor reflex from weak stimulation is normal but becomes greatly exaggerated when strong stimuli are used. This amounts to a complete reversal of the normal reaction. In this group of experiments the same results were obtained from brachial and sciatic stimulation.

5. A comparison of the effects of the same lesions on the conduction of pain and on the reflex changes in respiration and blood pressure shows that the afferent spinal path involved in the pressor reflex cannot be the same as the path for conscious pain nor the same as the afferent path to the respiratory center. On the other hand it is possible that the afferent spinal path involved in the depressor reflex is the same as that involved in reflex changes in respiration, and in the conduction of pain.

6. None of the lesions (lateral hemisection, posterior hemisection, section of the posterior funiculus, destruction of the apices of the posterior horn) had any noticeable effect on the conduction of pain in these cats.

7. It seems probable that there are two separate afferent spinal paths involved in the vasomotor reflexes: the pressor path, equally bilateral or chiefly homolateral in the apices of the posterior horn; and the depressor path chiefly crossed and located in the lateral funiculus.

It is a pleasure to acknowledge our indebtedness to Professors McGuigan and Hoskins for many helpful suggestions which we have received from them during the progress of this investigation.

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RHYTHMICAL CONTRACTION OF THE SKELETAL MUSCLE TISSUE OBSERVED IN TISSUE CULTURES

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The following observations upon the skeletal muscles of chick embryos in tissue cultures show that isolated fibers and myoblasts possess the property of automatic, rhythmical contractility, in the medium employed.

Among a number of preparations of myotomes of the tadpole explanted into frog lymph, Harrison (3) noticed, in a few instances when the myotome was thin, the differentiation within the myotome of the primitive myoblast into a cross striated fiber. He states that such fibers do not contract unless a part of the neural canal remains attached to the explanted myotome. This result of Harrison may be due to the fact that lymph was used as a medium in consequence of which the necessary salts to stimulate the muscle fiber may not have been present, or it may have been due to the fact that Harrison was dealing only with the myoblast within the thick explanted myotome and not with myoblasts and muscle fibers, which had grown out into the surrounding medium. The following observations show that in the case of the chick skeletal muscle, it may contract rhythmically when no nerve tissue is present. It is interesting to note that Harrison observed the primitive myoblast differentiate into the striated muscle fiber, since Champy (2) finds that the striated muscle fiber of the rabbit, when explanted into plasma, dedifferentiates into an indifferent mass of cells, through which the scattered remains of the myofibrillae can be observed. Champy does not state whether the muscle tissue contracted rhythmically at any time during this process.

Burrows (1), described the rhythmical contraction of an isolated heart muscle cell at the periphery of the growth of a tissue culture in a plasma medium. Burrows states also that a group of heart muscle cells, which had divided and differentiated from cells of the explanted piece, but which had become entirely separated from the other growth and

also from the explanted piece, continued to beat rhythmically, although with a changed rhythm from that of the old piece. The explanted piece of embryo chick heart may contain ganglion cells from which nerve fibers may grow, but such nerve fibers are so easily distinguished among or over the cells of the new growth, that it is possible to determine at a glance whether the preparation contains nerve fibers or not. In the case of the isolated heart muscle cell, which Burrows observed in rhythmical contraction, it is needless to state, there was no possibility of nervous influence. These observations of Burrows determine that it is possible for a heart muscle cell to contract rhythmically when entirely free from the nervous system and subject only to the stimulus of the surrounding plasma medium.

Rhythmical contraction of muscle tissue independent of nerve influence has been demonstrated by means of numerous physiological experiments among which some of the well known observations are those of Howell, Loeb, Stiles and Lingle.

Howell (4) found that

> a strip of vena cava from the heart of the terrapin may be kept in continuous rhythmic pulsation during forty-eight hours or more when immersed in baths containing only the inorganic salts, sodium chloride, potassium chloride and calcium chloride. Under normal conditions the stimulus that leads to a heart contraction is dependent upon the presence of calcium compounds in the liquids of the heart, but for rhythmic contractions and relaxations a certain proportion of potassium compounds is also necessary. The sodium chloride seems to be essential only in preserving the osmotic relations between the tissue and the surrounding liquid.

Loeb (9), observed that the skeletal muscle of a frog contracted rhythmically when placed in a 0.7 per cent solution of sodium chloride. Loeb concluded from his observations that it is only the antagonistic action of the calcium and magnesium salts of the blood, which prevent the skeletal muscles from contracting rhythmically.

> The solutions of Na-salts produce rhythmical contractions only if the muscle cells contain Ca-ions in sufficient number. As soon as there is a lack of Ca-ions in the tissue the Na-ions are no longer able to cause rhythmical contractions. On the other hand, if we add Ca-salts in sufficient quantity to the NaCl solution, it will no longer cause rhythmical contraction in a fresh muscle of the frog. It therefore looks as if the presence of a certain quantity of Na-ions caused contractions, but if the quantity of the Na-ions becomes too great in proportion to the Ca-ions, the muscle loses its irritability. On the other hand if there are too many Ca-ions present the rhythmical contractions become also impossible.—Loeb.

Stiles (10) showed that rhythmic contraction can be set up in the smooth muscle of the oesophagus of the frog. His conclusions correspond more with Howell's than with those of Loeb, i.e., he finds that the calcium salts have a direct action in the stimulation of the smooth muscle cells to contraction.

While a strip of smooth muscle in a 0.7 per cent solution of sodium chloride may contract irregularly for about an hour, in a Ringer's solution it will contract rhythmically for many hours. When the strip comes to rest in Ringer's solution, it can be again stimulated by successive quantities of calcium until the calcium chloride reaches 0.1 per cent when the calcium becomes depressive if not toxic. The calcium and potassium are both necessary to maintain rhythmic contraction for any length of time, but the sodium is the necessary salt, although the muscle frequently fails to contract at all in the sodium solution until the calcium is added.

Lingle (7) (8), described the rhythmical contractions of the isolated ventricle of a tortoise heart which does not beat in the blood when placed in pure sodium chloride solution. If the ventricle remains in a sodium chloride solution it ceases to beat. The pure solution of sodium chloride acts as a poison. A small amount of calcium however acts antagonistically to the injurious action of the sodium chloride. Calcium cannot start the contraction of the ventricle, but it is necessary to maintain the rhythmical contraction started by the sodium chloride.

The above together with other later work shows that it is possible for any muscle (heart, smooth or skeletal) to contract rhythmically, provided the necessary salts to stimulate the muscle to contraction are present in the tissue itself and in the surrounding medium.

In the following observations tissue cultures were made from pieces of the legs of 4, 5, 6, 7, 8, 9 and 10 day chick embryos, explanted into Locke's solution +0.5 per cent dextrose +10 per cent boullion according to the method of Lewis and Lewis (5) (6).[1]

The growth of cells is rapid and luxuriant, anywhere from one to fifty muscle fibers may have grown out radially from the explanted piece at the end of 24 hours (fig. 1). Also numerous isolated fibers

[1] Most of the failures to obtain growth in tissue cultures in Locke's solution by other observers is probably due to some error in their technic, as I have found it possible to obtain as large a growth in Locke's solution as in plasma. Dr. C. C. Macklin has shown that certain attempts to obtain growth have proven unsuccessful because evaporation of the medium has caused too great a concentration of the medium (unpublished).

and many primitive myoblasts are scattered throughout the new growth. There is an abundant growth of connective tissue and primitive mesenchyme cells. These cells are larger than the myoblasts and contain a larger nucleus. They extend further away from the explanted piece than most of the muscle cells. The connective tissue cells divide rapidly by mitosis and in some cultures the greater number of the connective tissue cells are in some phase of mitosis. Amitosis has never been observed in these cultures but mitotic figures are to be seen on all sides, frequently as many as one mitotic figure to every four or five resting cells. An attempt has been made to count the mitotic figures present in the growth at a given time and frequently more than 100 such figures have been present in one preparation at the same time.

Numerous myoblasts are always present in the growth which develops from an explanted piece of embryo chick leg of any of the above ages (4, 5, 6, 7, 8, 9 and 10 days) and the greater number of the fibers are less differentiated than is normal for a chick embryo of the age from which the explantation was made. Certain cultures have been kept in a healthy condition (many mitotic figures) for 10 and 12 days by frequently washing with the culture medium and in these cultures the muscle fibers redifferentiate somewhat, but a typical striated muscle fiber has never been observed in any growth, not even in that from a more adult chick embryo.

Nerve fibers do not grow out from the explanted piece of chick embryo leg and a nerve fiber has never been observed in any of the tissue cultures used for this study of skeletal muscles.

Mitotic figures are not present in the multinucleated muscle fibers (fig. 2) but the isolated myoblasts which contain a single nucleus frequently divide by mitosis. This division results in two typical myoblasts and not in an indifferent tissue such as that described by Champy.

The muscle fiber has the appearance of a gigantic cell with from 2 or 3 to as many as 60 or more nuclei in a spread out protoplasmic end of the muscle fiber (fig. 2). In a few instances such a protoplasmic end has split up into numerous myoblasts with each a single nucleus. These myoblasts migrate away and divide by mitosis.

A description of the growth and differentiation of the skeletal muscle in tissue culture will appear in a separate paper.

Fig. 1

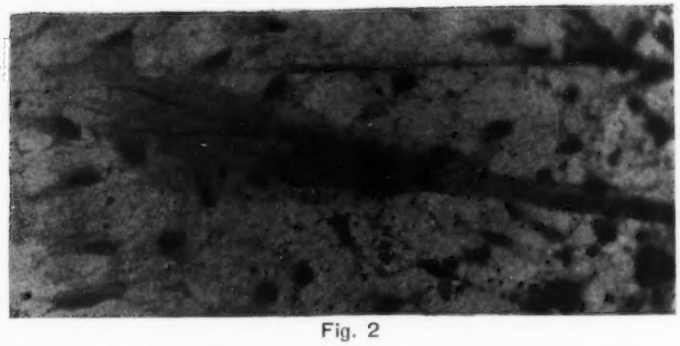

Fig. 2

Fig. 1. Muscle fibers and connective tissue of a 72-hour growth from an 8-day chick embryo wing in Locke's solution + 0.5 per cent dextrose + trace of yolk. Zenker fixation. Mallory stain. Oc. 4. Obj. 16.

Fig. 2. Protoplasmic end of a single muscle fiber, which contains many nuclei and primitive myofibrillae. Same culture as figure 1. Oc. 4. Obj. 4.

Fig. 3

Fig. 4

Fig. 3. Isolated muscle fiber, which contracted 120 times a minute for 8 hours. A 56-hour growth from a 9-day chick embryo leg in Locke's solution + 0.5 per cent dextrose + 10 per cent chicken bouillon. Zenker fixation. Mallory stain. Oc. 4. Obj. 4.

Fig. 4. Two living myoblasts, which contracted slowly (cell 1 once in 15 seconds, cell 2 once in 23 seconds) for one-half hour. Five-day growth from a 6-day chick embryo leg in Locke's solution + 0.5 per cent dextrose + 10 per cent chicken bouillon. Oc. 4. Obj. 4.

RHYTHMICAL CONTRACTION

Among the numerous muscle fibers present in the growth in a tissue culture, one may occasionally contract rhythmically. The time interval of the rhythmical contraction has been different for each muscle fiber as well as for each myoblast that has so far been observed to contract. Some fibers contract very rapidly, i.e., as often as 120 times a minute; others contract once in 2 or 3 seconds; others not oftener than once in 15 or 20 seconds; and some contract very infrequently, i.e., only as often as once in from 1 to 5 or 10 minutes.

Figure 3 is a photograph of an isolated multinuclear muscle fiber, which was not only free from the explanted piece, but also free from other muscle fibers. This fiber was first observed in rhythmical contraction when the culture was 48 hours old and it continued in rhythmical contraction (120 times a minute) throughout the day, at the end of which time it was fixed and stained. The stain used was Mallory's connective tissue stain and the primitive myofibrillae can be seen to extend from one end of the fiber to the other. The growth was from the leg of a 9-day chick embryo and was 56 hours old when fixed. The muscle fibers of the explanted piece were without doubt striated at the time of explantation and therefore it seems reasonable to suppose that this fiber must be either the result of dedifferentiation of the striated muscle fiber (Champy) or of the differentiation of a myoblast.

Figure 4 is a drawing of two living myoblasts during the resting period of a rhythimcal contraction which continued for over half an hour after it was discovered in a 5 days' growth from an explanted piece of a 6-day chick embryo. The time interval of contraction was different for the two cells. Cell 1 contracted every 15 seconds and cell 2 every 23 seconds.

Some well developed muscle fibers with a few cross striated myofibrillae have been observed to contract, but more frequently the property of rhythmical contraction is exhibited by less well developed muscle fibers such as figures 2 and 3 or by the isolated myoblast itself.

The ability of the muscle fiber to contract is not determined by the age of the culture for rhythmical contraction has been observed in cultures from 24 hours to 5 days old. Also the property of contractility is never general for any one culture, i.e., while one or two myoblasts

or muscle fibers of a given culture may contract, the other 50 or more fibers appear inactive or else the time interval of contraction is so slow that it is not observed.

EXPERIMENTAL WORK

An attempt has been made to stimulate the muscle fibers to contract by a change in their environment such as has been shown to stimulate rhythmical contractions by Howell, Loeb, Stiles and others.

The cover slip on the underside of which was the growth to be experimented upon was removed from the vaseline ring and a drop of a different solution at 39° C. was placed upon the growth. The cover slip was then replaced on a hollow ground slide and the growth was studied under the microscope in a warm chamber with the following results.

Sodium chloride. A drop of 0.9 per cent solution of NaCl in distilled water placed upon the growth in a few instances resulted in the immediate contraction of one or more of the muscle fibers. This contraction was repeated a few times and then ceased and did not occur again. In no case did the solution of NaCl stimulate a rhythmical contraction of all the muscle fibers or cells of the new growth. The muscle cell or fiber, which had previously been contracting, continued to contract for a short time and then ceased. It is possible that the NaCl penetrated the extremely thin growth very rapidly and had a toxic action upon the cells. If the NaCl solution was replaced by one which contained $CaCl_2$ as well as NaCl no change occurred. When the growth was again bathed in the medium, which had been used for the explantation (Locke's sol. + 0.5 per cent dex. + 10 per cent bouillon) the growth sometimes recovered and mitosis continued, but more frequently the growth became degenerate.

Calcium chloride. A drop of .025 per cent $CaCl_2$ resulted in the degeneration of the muscle fibers and other cells. A drop of Locke's solution had no effect, i.e., the muscle fiber continued to contract but the inactive fibers were not stimulated to contract. A drop of Locke's solution, which contained an increased amount of $CaCl_2$ either had no effect or resulted in the degeneration of the growth.

Dilution of the medium. A slight dilution of the medium used for the explantation had no definite action upon the contractility of the muscle tissue. A dilution of 10 per cent or more frequently stimulated certain of the muscle fibers and cells to contract, although it also resulted in the degeneration of many of the muscle fibers. The degeneration of the muscle fibers in this case was quite different from that

which usually takes place due to other causes. In this case the entire muscle fiber flowed from one extremity to the other and left no trace of its previous elongated structure. The mass of coarsely granular protoplasm which resulted from the rounding up of the muscle fiber later disintegrated.

Although the method used to stimulate the muscle tissue in these tissue culture growths to rhythmical contraction have so far not been successful, due probably to the fact that the method used was not sufficiently delicate, nevertheless the fact remains that by some so far unknown change, either in the tissue itself or in the surrounding medium, the myoblast and also the muscle fiber of the skeletal muscle of the chick embryo possess the property of rhythmical contractility when entirely free from nerve influences and subject only to the stimulus, which emanates from its environment.

It is interesting to note that the muscle cells inherit this property from cell to cell even when several generations of cells have taken place in a simple Locke's solution. The cytoplasm of the myoblast is quite different from that of the surrounding connective tissue cells. It is less thinly spread out and has a different refraction from the other cells.

CONCLUSION

The skeletal muscle tissue which grows out from an explantation of a piece of embryo chick leg into Locke's solution +0.5 per cent dextrose +10 per cent chicken bouillon, may contract rhythmically in the absence of nervous tissue.

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